Studies in the Synthesis of Benzoxazole Compounds

by
Dewald Kleinhans

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Supervisor: Dr GE Arnott

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DECLARATION

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December 2015

SUMMARY

Benzoxazoles are an important class of π-electron-excessive, benzene-fused heterocyclic compounds found in natural products and display a wide range of pharmacological applications. It is therefore a widely used starting scaffold for drug and agrochemical discovery programs. Other applications include: chiral auxiliaries in asymmetric reactions, chiral receptors for the resolution of racemic mixtures, fluorescent whitening dyes, various photochromic materials and as ligands for a wide range of catalytic reactions. Due to our interests in resorcinarenes, we came across 4-hydroxybenzoxazoles, a structural motif that has not been explored as potential asymmetric ligands. In this thesis it was attempted to investigate the synthesis, functionalisation and coordination chemistry of these compound class and finally look at a method of synthesising chiral 4-hydroxybenzoxazoles from amino acids.

A small library of achiral 4-hydroxybenzoxazoles were synthesised in good yields. These compounds were then reacted with various transition metals, of which only the Pd-salts proved to return any usable compounds. The first structural evidence of the bonding of 4-hydroxybenzoxazoles was recorded from single crystal X-ray diffraction analysis of the coordination compounds that formed. Different coordination modes were recorded, depending on the ligand and the Pd-salt used. The $PdCl_2$ compounds were also tested for catalytic activity with a Heck reaction, showing good conversions for the reaction between iodobenzene and styrene to form stilbene. Further examination pointed to the ligands playing an insignificant role in the reaction and the products possibly due to only the $PdCl_2$'s reactivity.

During this period it was also attempted to functionalise the phenol group with P(III) groups and repeat the coordination and catalytic studies. Efforts to synthesise these compounds were not successful, with oxidation of the P(III) to P(V) groups or degradation of these compounds. Efforts to synthesise these via phosphorous protection, utilising BH_3 or the *in situ* trapping of the compounds with transition metals, were also not successful. During the trapping experiments the phosphinite and Pd-salt formed a re-arranged product that is a known and useful catalyst on its own.

Finally a small library of chiral benzoxazoles and 4-hydroxybenzoxazoles were synthesised, starting from amino acids and utilising a Mitsunobu reaction to perform the ring closing. Antimicrobial tests with these compounds did not return any appreciable results.

OPSOMMING

Bensoksasool is 'n belangrike klas van π-elektron-ryk, benseen-saamgesmelte heterosikliese verbindings wat in natuurlike produkte voorkom en 'n wye verskeidenheid van farmakologiese funksies vertoon. Dit is dus 'n baie algemene basis struktuur vir dwelm- en landbouchemiese ontdekkings programme. Ander gebruike sluit in: chirale ligande in asimmetriese reaksies, chirale reseptore vir die resolusie van rasemiese mengsels, fluoresserende verwittings kleurstowwe, verskeie fotochromiese materiaal en as ligande vir 'n wye verskeidenheid van katalitiese reaksies. As gevolg van ons belangstelling in resorsinarene, het ons op 'n strukturele motief afgekom wat nog nie ondersoek is as potensiële asimmetriese ligande nie, die 4-hidroksiebensoksasole. In hierdie tesis is gepoog om die sintese, funksionalisering en koördinasie chemie van hierdie klas verbindings te ondersoek en uiteindelik 'n metode te ontwikkel om die sintese van chirale 4-hidroksiebensoksasole vanaf aminosure te bewerkstellig.

'n Klein biblioteek van achirale 4-hidroksiebensoksasole was gesintetiseer in goeie opbrengste. Hierdie verbindings was toe behandel met verskeie oorgangsmetale, waarvan slegs die Pd-soute enige bruikbare verbindings gevorm het. Die eerste strukturele bewyse van die binding van die 4-hidroksiebensoksasole is aangeteken met behulp van enkelkristal X-straaldiffraksie ontleding van die koördinasieverbindings wat gevorm is. Verskillende koördinasie mode is aangeteken, afhangende van die ligand en die Pd-sout wat gebruik was. Die $PdCl_2$ verbindings is ook vir katalitiese aktiwiteit met 'n Heck reaksie getoets. Die reaksie het baie goeie omskakeling gewys vir die reaksie tussen iodobenseen en stireen na stilbeen. Verdere ondersoeke het getoon dat die ligande nie ‘n beduidende rol in die reaksie speel nie en die produkte moontlik slegs as gevolg van die $PdCl_2$ se reaktiwiteit is.

Gedurende hierdie tydperk was daar ook probeer om die fenol groep met P(III) groepe te funksionaliseer. Met die uitgangstowwe sou die koördinering en katalitiese studies herhaal word. Pogings om hierdie verbindings te sintetiseer was nie suksesvol nie, met oksidasie van die P(III) na P(V) groepe of afbreking van hierdie verbindings. Pogings om dit te sintetiseer via fosfor beskermingstegnieke, deur gebruik te maak van BH_3 of die *in situ* vasvang van die verbindings met oorgangsmetale, was ook nie suksesvol nie. Gedurende die vasvang eksperimente het die fosfien en $PdCl_2$ ‘n herrangskikkings-produk gevorm wat op sy eie ‘n bekende en nuttige katalisator is.

Ten slotte was 'n klein biblioteek van chirale bensoksasole en 4-hidroksiebensoksasole gesintetiseer, vanaf aminosure. Om die ringsluiting te bewerkstellig was ‘n Mitsunobu reaksie gebruik. Antimikrobiese toetse met hierdie verbindings het nie enige noemenswaardige resultate opgelewer nie.

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A research project like this cannot be undertaken if you don't have the support and tutelage of a truly passionate teacher and mentor. That is why I first and foremost want to thank Dr. Gareth Arnott for the countless hours spent on teaching me not only the finer details of chemistry, but also of life. Thank you for your constant motivation, patience, support, honesty and the needed stern word if the situation required it. Sorry it took so long to finish this…

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LIST OF TECHNICAL ABBREVIATIONS

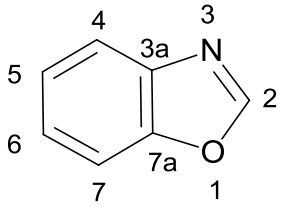
FT-IR	Fourier transform infrared spectroscopy
NMR	Nuclear magnetic resonance
ATR-IR	Attenuated total reflection infrared spectroscopy
ESI	Electrospray ionization
GC-MS	Gas chromatography–mass spectrometry

CHAPTER 1

Introduction

1.1 Review of Benzoxazole Chemistry

Benzoxazoles (Figure 1.1), also known as benzo[*d*]oxazoles or 1,3-benzoxazoles, are an important class of π-electron-excessive, benzene-fused heterocyclic compounds. Some reactions of benzoxazoles occur analogous to that of oxazoles, mainly due to the N-atom's electronegativity: salt formation and quarterisation occur at the ring nitrogen; electrophilic substitutions (e.g. nitration or halogenation) takes place on the benzene ring on the 5- or 6-position (the latter the preferred site) and nucleophilic attack occurs at the 2-position. Due to this, nucleophilic substitutions of 2-halobenzoxazoles also take place very easily.[1, 2]



1.1

Figure 1.1 Example of benzoxazole (**1.1**) with numbering.

The benzoxazole structure is found in natural products and displays a wide range of pharmacological applications. It is therefore a widely used starting scaffold for drug and agrochemical discovery programs.[3-5] Examples of natural products include the anti-mycobacterial Ileabethoxazole[6] and cytotoxic UK-1,[7] AJI9561,[8] Salvianen[9] and Nakijinol B[10] to mention a few (see Figure 1.2). Some examples of benzoxazoles in medicinal chemistry include the non-steroidal anti-inflammatory drug Flunoxaprofen,[11] HIV reverse transcriptase inhibitor L-697,661,[12] histone deacetylase inhibitor NK-HDAC-1[13] and the IMPDH inhibitor in *Cryptosporidium parvum* (**1.2** - Figure 1.2).[14]

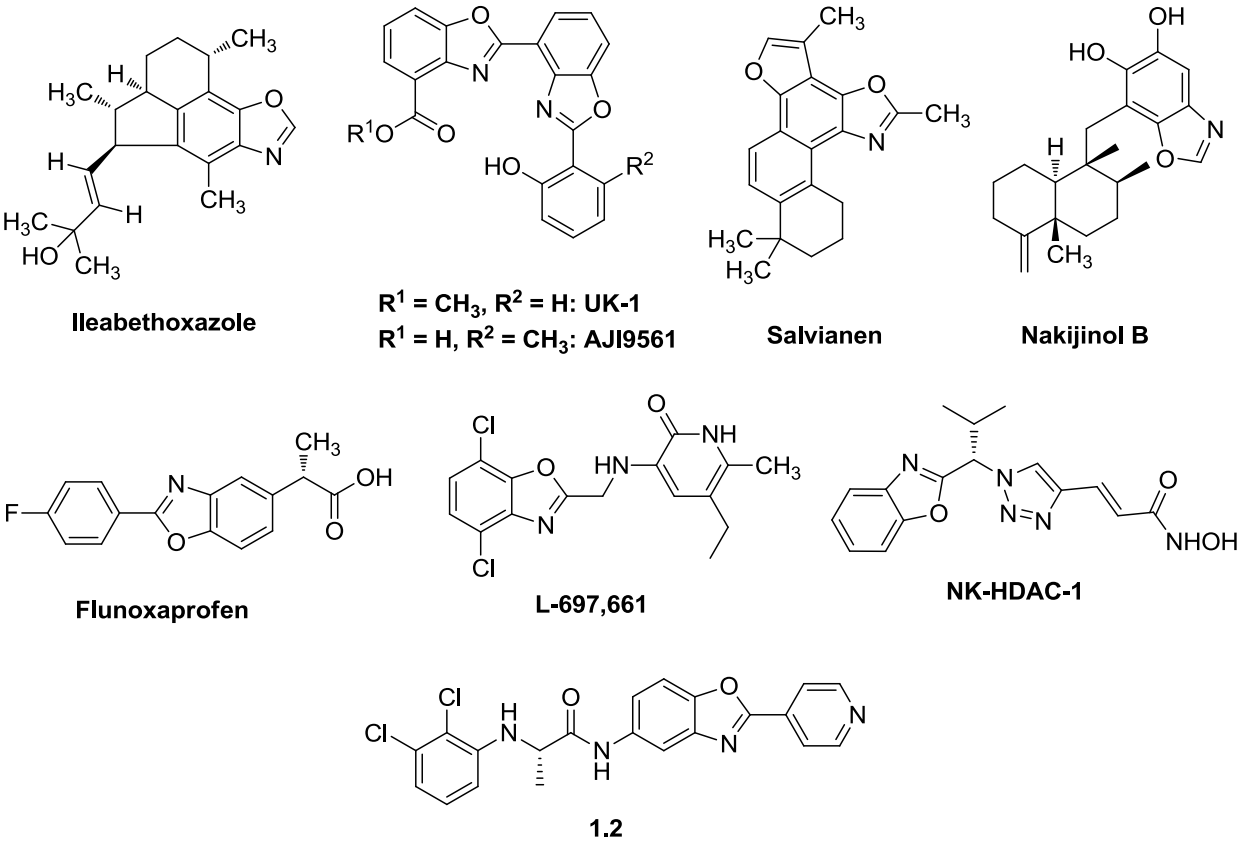


Figure 1.2 Some natural and synthetic benzoxazoles with varied pharmacological attributes.

The benzoxazole structure also been found in herbicides,[15, 16] chiral auxiliaries in asymmetric thermal reactions (e.g. Rebek's imine)[17-19] and chiral receptors for the resolution of racemic mixtures.[20-23] The strong luminescent properties of the benzoxazole ring also means that it plays a big role in fluorescent whitening dyes,[24] various photochromic materials[25] and mesogenic polymers/liquid crystalline networks.[26-28]

1.1.1 Coordination Chemistry and Catalytic Capabilities of Benzoxazoles

A large body of literature is available regarding benzoxazoles and their application as ligands in coordination chemistry. To fully cover this amount of work would be too detailed for the sake of this study and only some of the uses with examples that illustrate the necessary or different coordination concepts will be presented, with a special focus on the use of benzoxazoles as ligands in various catalytic reactions. A special part will also be dedicated to the coordination chemistry of 4-hydroxybenzoxazoles as ligands.

1.1.1.1 Introduction

In the late 1960's Duff and co-workers[29-32] performed a significant amount of the fundamental work on the coordination of benzoxazole **1.3** (Figure 1.3) and 2-methylbenzoxazole **1.4** (Figure 1.3) as monodentate ligands with various transition metals. Making use of a combination of IR spectroscopy, UV-VIS spectroscopy, conductivity data and inductive effects it was reasoned that benzoxazole **1.3** formed coordination compounds through the nitrogen atom (κ^1*N*), whereas the methyl variant **1.4** preferably coordinated through the oxygen atom (κ^1*O*). Peyronel *et al.*[33] on the other hand, argued that the IR spectroscopy data could also be interpreted as the compounds only forming κ^1*N* type bonding. Later work by Casu *et al.,*[34] making use of NMR spectroscopy and quantum-mechanical calculations on Pt(II) complexes, reinforced this argument. The question was finally unequivocally solved by Jones *et al.*[35] Making use of single crystal X-ray diffraction data and DFT calculations it was shown that both compounds coordinate to metals via κ^1*N* type bonding (see **1.5** in Figure 1.3). Another example (see **1.6** in Figure 1.3) of the monodentate bonding of benzoxazole derivatives were also reported by Ito *et al.*[36] The absence (thus far) of O-coordinated benzoxazole compounds further strengthened the argument of κ^1*N* type bonding.

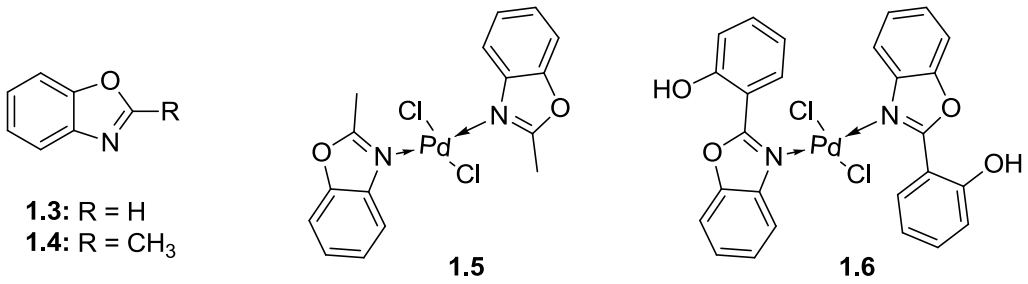


Figure 1.3 Benzoxazole (**1.3**) and 2-methylbenzoxazole (**1.4**), as well as an example of the κ^1*N* type bonding in as seen in the square planar **1.5** and **1.6**.

1.1.1.2 Benzoxazole coordination compounds in medicinal applications

In 2007 Kumar *et al.*[37] reported the synthesis of a library of 2-(1'/2'-hydroxynaphthyl) benzoxazoles and their coordination with metals [Mg(II), Fe(II), Co(II), Ni(II), Zn(II) and Cd(II)] in a ligand to metal ratio (L:M) of 2:1 (see Figure 1.4 **1.7** and **1.8** for examples of the complexes formed). Making use of elemental analysis, UV, IR and mass spectroscopy it was deduced that complexes were formed where both the nitrogen and phenol were involved in the binding, forming square planar complexes with two six-membered rings. These complexes showed good antimicrobial and antifungal properties.

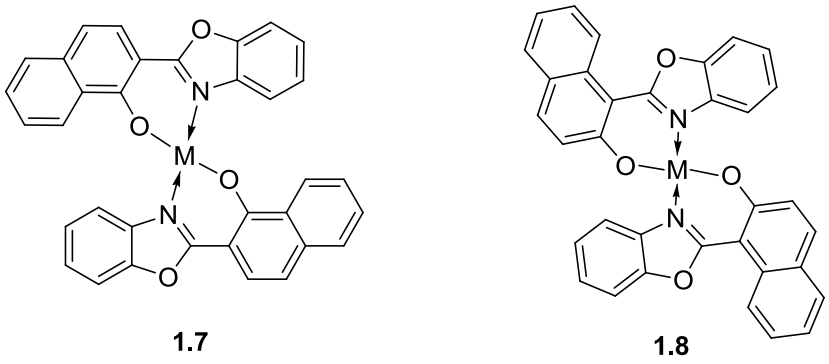


Figure 1.4 2-(1'/2'-hydroxynaphthyl)benzoxazoles complexes **1.7** and **1.8** [M = Mg(II), Fe(II), Co(II), Ni(II), Zn(II) and Cd(II)]

Making use of elemental analysis, UV, IR, NMR and mass spectroscopy Samota and Seth showed that, depending on the functional group on their 2-(2') substituted benzoxazole, that different coordination modes were possible in the reaction with Pd(II) and Pt(II) salts (Figure 1.5) and the benzoxazole ligands.[38] The 2(2'-hydroxyphenyl) **1.9** and 2-(2'-mercaptophenyl) **1.10** derivatives formed complexes akin to that was shown in Figure 1.4, with the phenol and mercaptophenol moieties forming bonds with the metal. In the case of the 2-(2'-aminophenyl) derivative **1.11**, coordination without deprotonation was observed, thus acting as a bidentate ligand. All the compounds were square-planar and showed some antimicrobial activity.

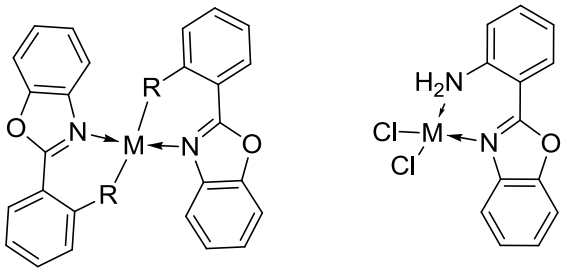
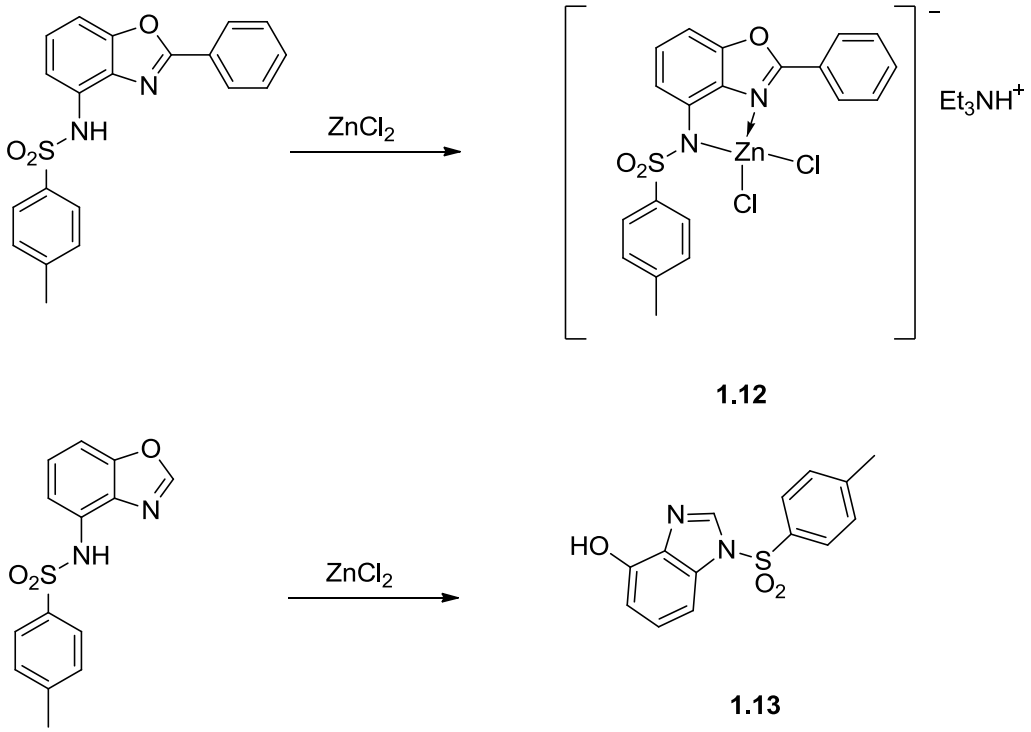


Figure 1.5 Different coordination complexes formed with 2-substituted benzoxazole ligands (M = Pt/Pd).

As part of their study to find matrix metalloproteinase inhibitors, Cohen and co-workers synthesised a library of sulfonamide benzoxazoles and formed metal complexes with them.[39] The complexes were analysed with single-crystal X-ray diffraction methods to better understand the coordination chemistry of these compounds, which is directly relevant to their ability to act as metalloproteinases.

Treatment of the benzoxazole sulfonamide moieties with metal salts [Zn(II), Co(II), Ni(II) and Cu(II)] returned vastly different results (Scheme 1.1). The reaction of the 2-phenyl derivative with $ZnCl_2$ lead to a anionic mononuclear complex **1.12**, with a slightly distorted tetrahedral Zn(II) ion coordinated by two chloride ligands and one molecule of the ligand. The ligand was coordinated to the Zn through its imine and deprotonated sulfonamide nitrogen atoms. A protonated triethylamine molecule served as the counter ion in the crystal lattice. Attempts to form other metal complexes with the 2-phenyl ligand through crystallisation were unsuccessful.



Scheme 1.1 Reactions of sulfonamide benzoxazoles with [$ZnCl_2$]

Treatment of the benzoxazole derivative (R = H, Scheme 1.1) returned not the expected coordinated complex, but 3-tosyl-7-hydroxybenzimidazole **1.13**, a result that was confirmed when the ligand was treated with other Zn(II) salts. It was argued that the benzoxazole ring was unstable in the presence of the Zn(II) ions, and rearranged to **1.13**, which incidentally coordinated better with the Zn(II) salts, forming a [$Zn_4Cl_2L_6$] cluster. Complexes also formed readily when reacted with the other metals. In all the cases the ligand was only binding through the imine nitrogen atom and the sulfonamide group was not deprotonated. The Co(II) and Ni(II) complexes formed mononuclear complexes with a distorted octahedral geometry. The equatorial plane comprised of two chelating acac (acetylacetonate) ligands and the axial positions occupied by two monodentate benzoxazole molecules. With

$Cu_2(OAc)_4$ a paddle-wheel, dinuclear complex was formed with two benzoxazole ligands on the axial positions.

The benzoxazole structural motif was also included in a triptycene-based ligand used in the modelling of the carboxylate-bridged di-iron enzyme active sites to good effect.[40]

1.1.1.3 Benzoxazole ligands in catalytic palladium C-C forming reactions (Heck, Suzuki, etc.)

In an effort to investigate phosphine-free Heck catalyst systems, Li *et al*.[41] synthesised Pd-complexes based on 2-arylnaphthoxazoles (Figure 1.6). The reaction of 2-arylnaphthoxazoles with $Pd(OAc)_2$ in acetic acid formed the cyclopalladated **1.14** derivatives in moderate yields and the structures were confirmed using single-crystal X-ray diffraction. These compounds, along with coordination compound **1.15**, were tested as catalysts for the Heck coupling of various aryl halides with ethyl acrylate and found to all show good catalyst activity. Palladacycle **1.14** (R = OCH_3) showed the greatest promise at a catalyst loading of 0.01 mol% in the optimised reaction conditions (K_2CO_3, DMF, *n*-Bu4NBr at 140 °C), even showing good reactivity towards aryl chlorides.

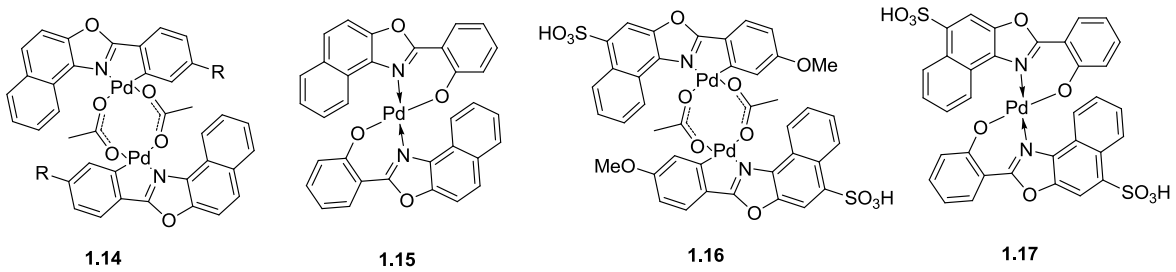
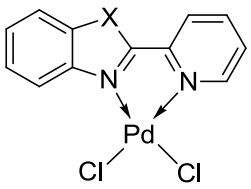


Figure 1.6 Complexes derived from 2-arylnaphthoxazoles used as phosphine-free Heck [**1.14** (R = H, CH_3, OCH_3), **1.15**] and Suzuki catalysts (**1.16, 1.17**).

The work was followed up by the synthesis of water soluble versions of the 2-arylnaphthoxazoles (see **1.16** and **1.17** in Figure 1.6).[42] These complexes displayed good reactivity as catalysts in the Suzuki coupling of various aryl halides with phenyl boronic acid, with a catalyst loading of 0.1 mol% at the optimised reaction conditions (K_3PO_4, H_2O, 100 °C in air).

Two different research groups also studied the Heck coupling reaction with complexes formed from 2-(2-pyridyl)benzazole derivatives as ligands. Hayashi and co-workers studied the ligand effects of a range of simple 2-(2-pyridyl)benzazole Pd(II) complexes **1.18**, making use of their X-ray crystallographic structures, ^{1}H NMR spectroscopy and catalytic activities in

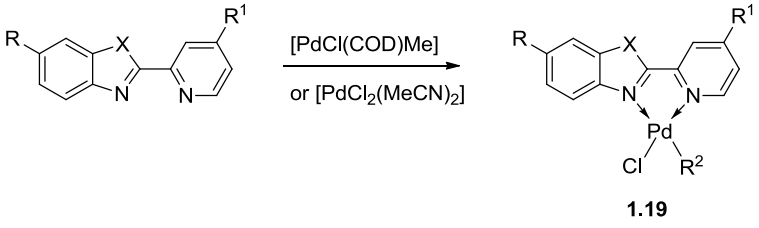
Mizoroki-Heck coupling reactions (Figure 1.7).[43] Utilizing the Mizoroki-Heck coupling of 4-bromotoluene and *tert*-butyl acrylate as a model system it was found that the benzimidazole derived compound (X = NH) was the most active, followed by the benzoxazole (X = O), benzothiazole (X = S) and lastly the *N*-methylated benzimidazole (X = NMe). Initial studies also pointed to the benzimidazole derived complex (X = NH) showing promise as a potential catalyst in the Sonogashira coupling of 4-iodotoluene and ethynylbenzene.



1.18

Figure 1.7 2-(2-Pyridyl)benzazole Pd(II) complexes (X = NH, O, S, NMe).

Ojwach *et al*.[44] also made use of derivatized mononuclear 2-(2-pyridyl)benzazole Pd complexes **1.19** (Scheme 1.2) in their studies towards the use of nitrogen heterocycles as ligands in C-C transformation catalysts, in this case for the Heck reaction. The catalytic activities of all the complexes were tested using the coupling of iodobenzene and butylacrylate as a model reaction. These catalysts performed very well at high temperatures and at low catalyst loading, it was shown that at 80 °C and a catalyst loading of 0.4% that it was still extremely active. Further experimentation also pointed to these as "living"* Heck coupling systems.



1.19

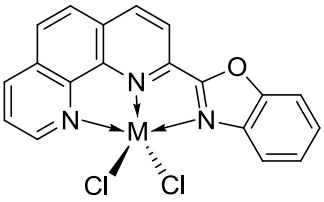
1.19a (R = R^1 = H, X = NH, R^2 = Me)
1.19b (R = R^1 = H, X = S, R^2 = Me)
1.19c (R = H, R^1 = ^{t}Bu, X = O, R^2 = Cl)
1.19d (R = H, R^1 = ^{t}Bu, X = O, R^2 = Me)
1.19e (R = H, R^1 = ^{t}Bu, X = S, R^2 = Cl)
1.19f (R = H, R^1 = ^{t}Bu, X = S, R^2 = Me)
1.19g (R = ^{t}Bu, R^1 = ^{t}Bu, X = S, R^2 = Me)

Scheme 1.2 Examples of the Pd complexes synthesized using derivatized 2-(2-pyridyl)benzazole ligands.

* The stability of the catalytic system was tested by adding equal amounts of base and substrate to the reaction at one hour intervals and letting it run for a period of time and accessing the conversion of substrates to products. The conversion after the fourth addition cycle remained the same and no deactivation of the complex was observed. The authors referred to this as a "living" catalytic system.

1.1.1.4 Benzoxazole ligands in catalytic polymerisation reactions

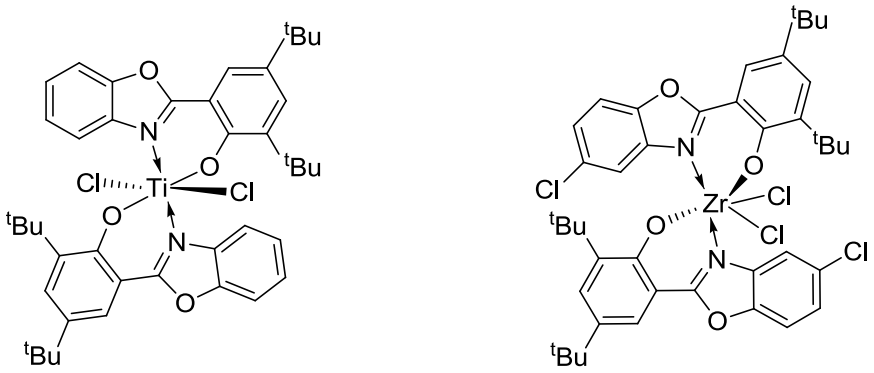
Zhang *et al.*[45] studied ethylene oligomerization making use of the tridentate 2-Oxazoline/benzoxazole-1,10-phenanthrolinyl complexes of nickel, cobalt and iron (see **1.20** in Figure 1.8 for examples of the complexes). The nickel complexes, with [$AlClEt_2$] as co-catalyst, revealed high activities for ethylene oligomerization. In contrast to this the cobalt and iron complexes, with MMAO as co-catalyst, showed reasonable activities for the same reaction. In all the cases it was remarked that the ligand and substituents on the ligand played a large role in the activity and selectivity of the catalyst.



1.20

Figure 1.8 An example of the 2-benzoxazole-1,10-phenanthrolinyl complexes of nickel, cobalt and iron used in ethylene oligomerization reactions (M = Ni, Co, Fe)

Jin and Shi studied the structural and catalytic properties of titanium (**1.21**) and zirconium (**1.22**) complexes with salicylbenzoxazole ligands towards ethylene polymerisation (Figure 1.9).[46] Using MAO as co-catalyst it was found that the titanium complexes exhibited almost no activity. In contrast to this the zirconium complexes showed very good activity for ethylene polymerization as well as some activity in the oligomerization of 1-hexene. This study also found that steric hindrance and the electronic effect of the ligands remarkably affected the catalytic activities of the catalysts. Bulky substituents on the position ortho to the phenol caused the highest activities. It was also shown that substituents on the benzoxazole moiety also contributed to the activity of the compound, of which **1.22** performed the best [29.54×10^6 g of PE (mol of Zr)$^{-1}$ h^{-1} (mol/L of ethylene)$^{-1}$ over five minutes].

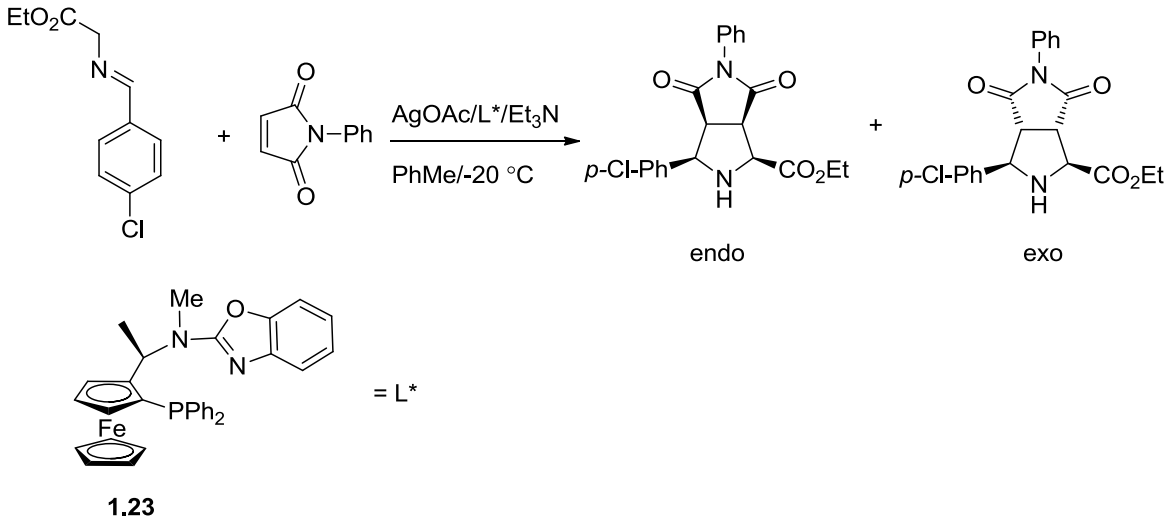


1.21 **1.22**

Figure 1.9 Titanium and zirconium salicylbenzoxazole complexes used in ethylene polymerisation.

1.1.1.5 Benzoxazole ligands in catalytic asymmetric reactions

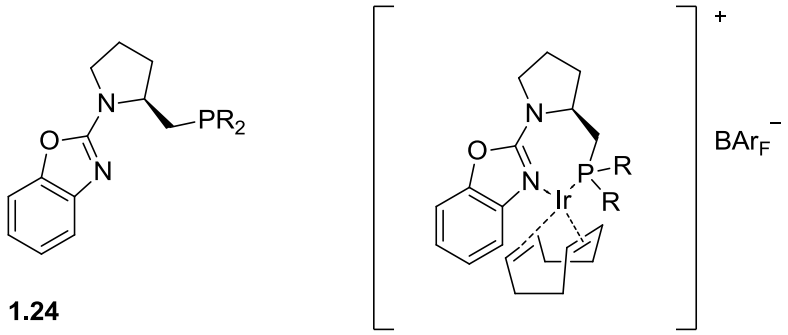
Making use of the 1-ferrocenylethylamine skeleton as a chiral ligand building block Yan *et al.*[47] decided to integrate benzoxazoles as a way of increasing the rigidity of their ligands. A range of chiral ferrocenyl phosphine–benzoxazole ligands were synthesized and their efficiency was tested in the Ag(I)-catalysed asymmetric [3+2] addition of azomethines and *N*-phenylmaleimide (see Figure 1.10 for an example of the reaction and ligands). These ligands revealed very good enantioselectivity for the *endo*-product (diastereoselectivity >95:5 for *endo:exo*) and ee's of >99% for some products. Further applications in asymmetric reactions are being looked into for these ligands.



1.23

Figure 1.10 Ag-catalyzed asymmetric [3+2] cycloaddition with a chiral ferrocene-based benzoxazole **1.23.**

Studying the asymmetric Ir-catalysed hydrogenation of tri-substituted alkenes, Pfaltz and Rageot made use of chiral P,N-benzoxazoles ligands, derived from proline (Figure 1.11).[48] These complexes showed moderate to good enantioselectivity, with ee's of >99% seen in some cases. The study also showed that the influence of the R-group on the phosphorous atom played a big role in the hydrogenation results, with the *tert*-butyl group proving to be overall the best.

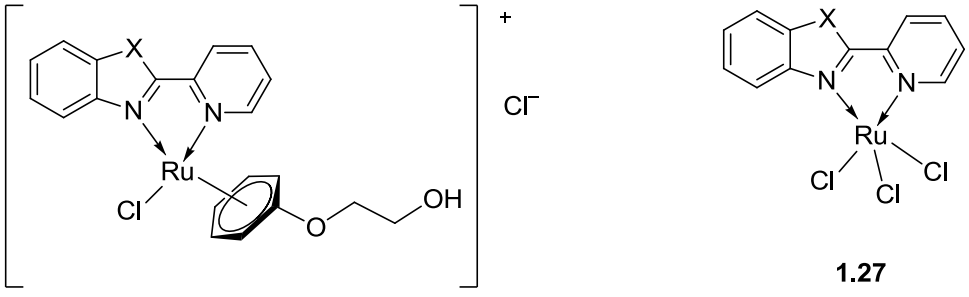


1.24 **1.25**

Figure 1.11 Examples of the ligands (**1.24**) and Ir-complexes (**1.25**) used for the asymmetric hydrogenation of tri-substituted alkenes (R = Ph, *o*Tol, *t*Bu, Cy).

1.1.1.6 Benzoxazoles used as ligands in miscellaneous catalytic reactions

Very recently, the research group of Ojwach elaborated on the use of 2-(2-pyridyl)benzazole ligands by testing their abilities as ligands in catalytic hydrogenation reactions of various moieties.



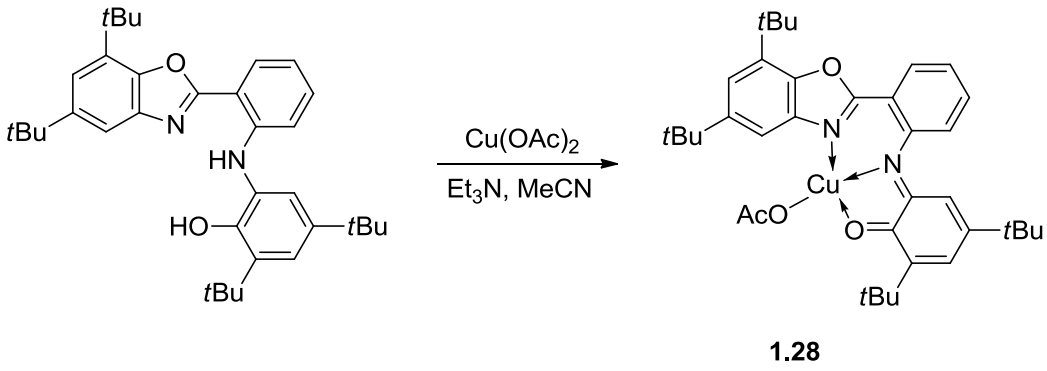
1.26 **1.27**

Figure 1.12 Examples of the Ru complexes used in the hydrogenation studies of Ojwach's group (X = NH, S, O).

Cationic Ru(II) complexes (Figure 1.12, **1.26**) were used as recyclable catalysts in the biphasic hydrogenation of alkenes and alkynes to good effect.[49] Ru(II) and Ru(III) complexes

(Figure 1.12, **1.27**) were also used for the transfer hydrogenation of ketones and 2-propanol, the benzimidazole ligands proving to be the most reactive and the benzoxazole ligands showing intermediate reactivity.[50]

Taking inspiration from biological systems Storr and co-workers synthesised a tridentate benzoxazole ligand to test in the Cu(II) catalysed oxidation of structurally diverse alcohols to aldehydes, with molecular oxygen as the oxidant.[51] The Cu(II) complexes revealed the formation of an interesting iminosemiquinone formation of the ligand during coordination to the metal (see Scheme 1.3). The group showed that the $Cu(OAc)_2$ derived complex generally provided better results than the $CuCl_2$ derived one and no over-oxidation to the carboxylic acid was observed. Acquaye and co-workers made use of Ru(III) complexes, together with *tert*-butylhydroperoxide as the oxygen source, to study the catalytic oxidation of sulfides to sulfoxides. These complexes showed moderate to good turnover values (90-125) depending on the substrate used. No over-oxidation to the sulfone was witnessed.[52]



1.28

Scheme 1.3 Synthesis of the complex **1.28** used in the catalytic oxidation of alcohols to aldehydes. Note the iminosemiquinone formation upon coordination.

More cases where benzoxazoles play a role as a ligand in catalytic reactions are also available for the interested reader.[53-59]

1.1.1.7 Summary

From this brief overview it can be seen that benzoxazoles have a wide range of interactions with various transition metals, with different coordination chemistry modes. The use of these ligands in catalysis is also a subject that is slowly starting to gain momentum and already a wide range of uses are available. More examples of benzoxazoles used as ligands (see Figure 1.13) are available for the interested reader.[60-71]

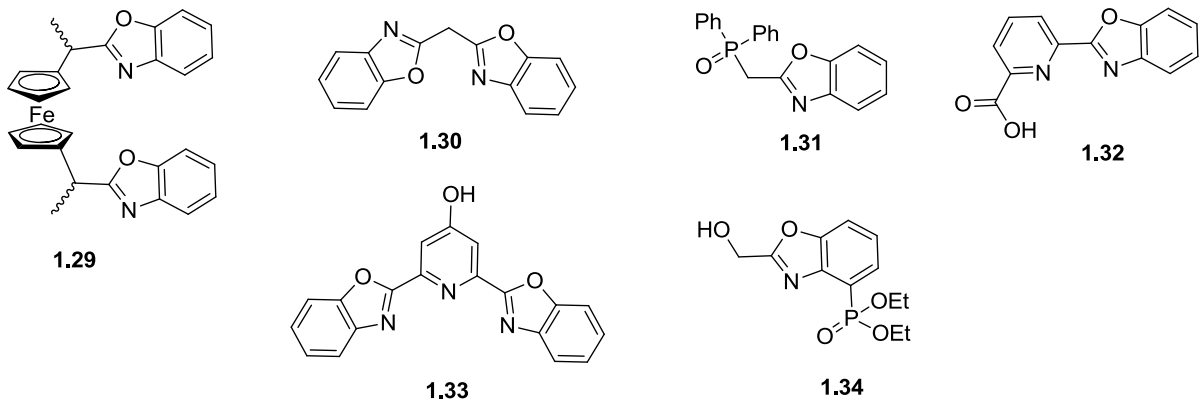


Figure 1.13 Other examples of benzoxazole ligands.

The focus will now turn to the use of 4-hydroxybenzoxazoles as ligands in coordination chemistry.

1.1.1.8 The coordination chemistry of 4-hydroxybenzoxazoles

In the early 1950's, Fallab[72] and Sorkin *et al.*[73] independently looked at the role of Cu(II) ions and 8-hydroxyquinoline derivatives during their investigations into the inhibition of bacteria, in particular *Mycobacterium tuberculosis*. During their studies, 4-hydroxybenzoxazole (Figure 1.14) was treated with Cu(II) solutions and it was only remarked that these reactions showed a positive result, implying that coordination had occurred. There was however no other mention made or data presented of possible coordination structures or bonding modes.

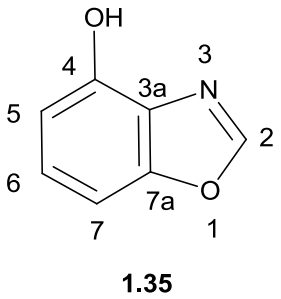


Figure 1.14 4-Hydroxybenzoxazole with numbering

Later studies by Beckett and Kerridge, during their investigation into the synthesis and antibacterial properties of 4-hydroxybenzazoles, more mention was made of the interaction of 4-hydroxybenzoxazole ligands and transition metals.[74] During the study it was remarked that all the compounds showed positive results when reacted with cupric and ferric ions, at a concentration of 0.5% in 70% aqueous ethanol. 2-Ethyl-and 2-methyl-4-hydroxybenzoxazole also formed precipitates with 0.05 N silver nitrate in a 0.05 N nitric acid solution. No more

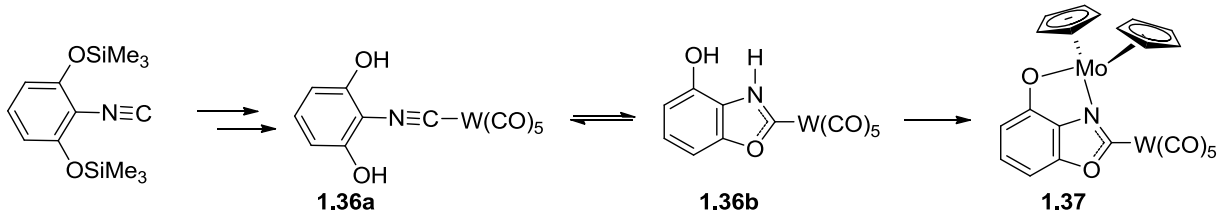
information was presented to give an indication of the exact nature of these reactions or products formed from them.

A few years later, in the early 1960's, Lane *et al.*[75] studied the acid dissociation and chelate stability constants for a range of oxine-type compounds, due to them being structural analogues of 8-hydroxyquinoline. The basicity of the 4-hydroxybenzoxazoles was the lowest and this was attributed to the higher electronegativity of the oxygen atom in the 1-position. These compounds also showed very low formation constants in their reaction towards metals [Cu(II), Pb(II), Zn(II), Ni(II) and Co(II) in ratios of 8:1 or 4:1 ligand:metal]. It was argued that a combination of factors was responsible for this of which the ligands' low basicity, the orientation of the donating electrons on the imine nitrogen and the distance/angles between potential chelating atoms not being favourable playing the biggest role in the poor results. No further structural evidence was given for an indication of the bonding modes that were taking place during chelate formation.

Resnik *et al.*[76] found discrepancies between their own work on the chelate stability constants of 4-hydroxybenzoxazole with Cu(II) salts and those of Lane and co-workers.[75] Their data and evidence of mixed valence complexes along with precipitate formation pointed to the possible oxidation of the phenol moiety of the ligand by the Cu(II) salts. This was confirmed to happen if there was another compound in solution that had strong Cu(I) chelating properties, leading to a redox reaction taking place between the 4-hydroxybenzoxazole and the Cu(II) metal centre in the complex. During this work no indication was given of the possible structural characteristics of the complexes.

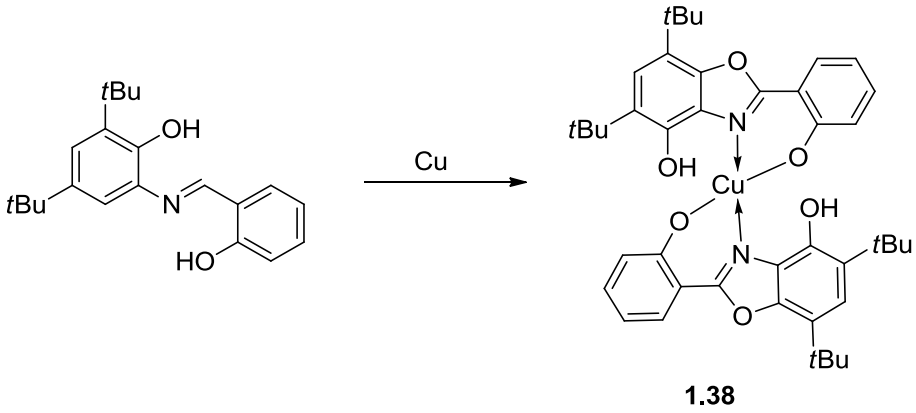
Starting from 4-hydroxybenzoxazole, and making use of well-established chemistry,[77] Hahn *et al.*[78] synthesised a heterobimetallic complex **1.37** (Scheme 1.4) in the early 2000's. The 2,6-bis(trimethylsiloxy)phenyl isocyanide, from 4-hydroxybenzoxazole, was treated with a tungsten complex and the silyl groups removed to form a mixture of carbene complexes **1.36a/b**. From the ^{1}H NMR spectroscopic analysis it was deduced that the two compounds exist in an equilibrium of 1:3, leaning to the 4-hydroxybenzoxazol-2-ylidene carbene **1.36b**. Treatment of **1.36b** with a base and a molybdenum precursor led to the formation of the heterobimetallic complex **1.37**, driven by the five-membered chelate-ring formation. X-ray crystallographic analysis of the final compound revealed a large distortion around the nitrogen atom and the bond lengths of Mo-O and Mo-N almost the same. It was argued that only metal centres with a large ionic radius would be able to form a bidentate complex in this fashion and confirmed by the non-formation of a similar titanium complex. 4-

Hydroxybenzoxazoles have also been used as starting material to synthesise isocyanide ligands in other cases.[79, 80]



Scheme 1.4 Synthesis of a unique heterobimetallic complex **1.37**.

During the study of Shmakova *et al.*,[81] on the di-nuclear chelates formed by chemical and electrochemical methods with *N*-(3,5-di-*tert*-butyl-2-hydroxyphenyl) salicylaldimines and cobalt, copper and nickel, an interesting by-product was recovered. Evaporation and crystallization of the mother liquors resulting from the electrochemical synthesis of the copper chelates led to the discovery of a 4-hydroxybenzoxazole based mono-nuclear complex **1.38** (Scheme 1.5).



Scheme 1.5 Electrochemical synthesis of **1.38** from Cu and *N*-(3,5-di-*tert*-butyl-2-hydroxyphenyl) salicylaldimines

The hetero-cyclisation of the Schiff base could be explained from previous work, but the formation of the phenol on the 4-position was not clearly understood. It seemed as if it was formed by a metal-promoted [Cu(II) in this case] hydroxylation of the heterocycle's aromatic ring, as comparative reactions have been seen in aromatic and aliphatic systems before.[82, 83] It was clear that the conditions of their synthesis (electrochemical) and the presence of the Cu(II) ions played a major role in the formation of the by-product. Coordination to the copper atom occurred via the imine and the 2-(2-hydroxyphenol) group, forming a complex akin to **1.9**. The phenol on the 4-position did not play a role in the coordination to the metal centre,

but formed a hydrogen bond with the 2-(2-hydroxyphenol) group, thus providing stability to the complex as a whole.

Some examples in the patent literature also exist, but no clear information is available about the coordination chemistry.[84, 85]

1.1.1.9 Conclusions

From the examples given some general observations can be made:

1) The benzoxazole moiety coordinates to metal centres through the imine nitrogen in the case of monodentate coordination
2) In multidentate systems quite a large part of the coordination chemistry of benzoxazole ligands depends on other coordinating group(s) attached to the 2-position, varying in size and complexity. The most popular groups are pyridine-, phenol-, phenylamine- and amine-derivatives.
3) Very few examples exist were bidentate coordination to a metal centre is formed by the nitrogen on the 3-position and a group on the 4-position of the benzoxazole.
4) The literature surrounding the synthesis and use of 4-hydroxybenzoxazole as ligands in coordination chemistry is very limited and presented a possible research focus.

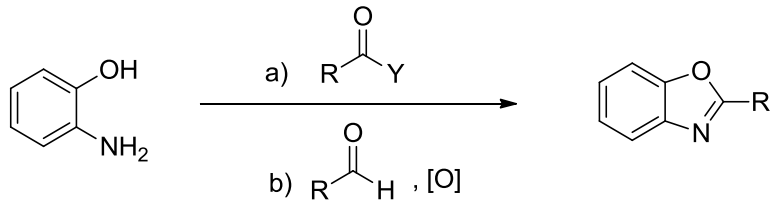
Attention will now be turned to the synthesis of benzoxazoles.

1.1.2 Synthesis of Benzoxazoles

The synthesis of benzoxazoles can be achieved using multiple approaches and constitutes a vast amount of literature that is expanding daily. To fully cover this amount of work would be too detailed for the sake of this study and only the main approaches with examples that illustrate the necessary concepts will be presented, with a special focus on the synthesis of chiral derivatives of benzoxazoles and that of 4-hydroxybenzoxazoles. Good overviews of the synthetic strategies in benzoxazole synthesis are available as a starting point for any inquiry.[1, 4, 86]

1.1.2.1 Standard Methods

Two of the most commonly used approaches to the synthesis of benzoxazoles can be seen in Scheme 1.6.



Scheme 1.6 Standard approaches to the synthesis of benzoxazoles (R = alkyl, aryl, H, etc.; Y = leaving group)

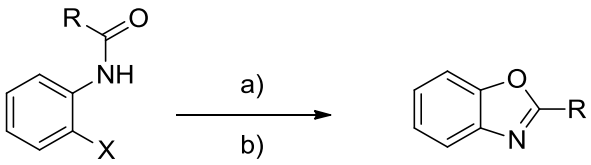
The first approach involves the direct condensation of carboxylic acid derivatives with the aminophenol derivative. These reactions are usually performed under strong acidic conditions, at high temperatures, neat or in solution (high boiling solvents like xylenes are commonly used). Some of the most widely used acids are polyphosphoric acid (PPA),[87-89] boric acid[90-92] and polyphosphate ester (PPE)[93] for milder reaction conditions. Recently the use of microwaves to perform the cyclisation reaction is getting more attention.[94] In some of the cases silica gel[95] and even Lawesson's reagent[96] is used to facilitate the reaction. Other examples of direct condensation includes the use of trialkyl orthoesters,[97-99] Deoxo-Fluor[100] and acid anhydrides[101] to name a few.

Although there is evidence of the direct formation of benzoxazoles by the reaction of aldehydes and aminophenols,[102] most of the reactions are hinged on the formation of an imine and subsequent oxidative cyclisation. Some of the most commonly used oxidants include DDQ,[103] dibenzoyl peroxide,[104] $PhI(OAc)_2$,[105] the Dess-Martin reagent,[106] *N*-bromosuccinimide,[104] lead (IV) acetate[107] and molecular iodine[108] and MnO_2/SiO_2[109] under microwave conditions. Most of these reactions can be performed under milder conditions than the first approach, which means that acid-sensitive functional groups can be handled with greater ease and more structural diversity can be included in the benzoxazole compounds.

1.1.2.2 Other approaches

A large part of the literature on the synthesis of benzoxazole compounds starts from the formation of a benzamide from aminophenols, making use of amide coupling reactions. In this manner a wide range of groups can be introduced to the 2-position of the benzoxazole in a very effective manner. The initial amide can then be cyclized via a few different methods (Scheme 1.7). As in the previous case the benzoxazole can be formed by heating the neat carboxamide to high temperatures (200-300 °C) and removing the water by-product by distillation or molecular sieves.[110] To facilitate the reaction and use milder reaction conditions, a dehydrating reagent, most commonly in the form of an acid catalyst, can be

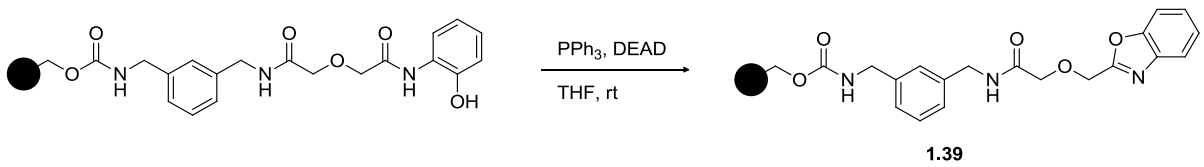
used. The most commonly used agents are again PPA,[111] PPE,[112] 4-toluenesulfonic acid[113-115] and the milder alternative pyridinium 4-toluenesulfonate.[112]



Scheme 1.7 Synthesis of benzoxazoles from 2-halo/phenolbenzanilides (R = alkyl, aryl): a) (X=OH) Using high temperature and/or dehydrating agents, b) (X=halide) Cu(I) catalyzed ring closing.

Recently it was also shown that benzoxazoles could be synthesised from the copper catalysed ring closing of 2-halobenzanilides (Scheme 1.7). Work by Batey and co-workers showed that using a combination of CuI (5 mol%), 1,10-phenanthroline (10 mol%) and Cs_2CO_3 resulted in the formation of simple and complex benzoxazoles in good to excellent yields.[3] They also showed in later work that benzoxazoles could be synthesised directly from the acyl chloride and 2-haloaniline in a copper-catalyzed domino annulation, by tweaking the reagents and performing the reactions under microwave irradiation.[4] Barbero *et al.*[116] showed that the reaction can also be performed in water as solvent, whereas Nagasawa and Ueda showed that benzoxazoles can be synthesized from the benzamide (Scheme 1.7, X = H) using $Cu(OTf)_2$ in an oxygen atmosphere in good yields.[117] To create a library of benzoxazole compounds with large diversity some authors have also made use of the multicomponent Ugi reaction, followed by copper catalysed ring closing.[118, 119]

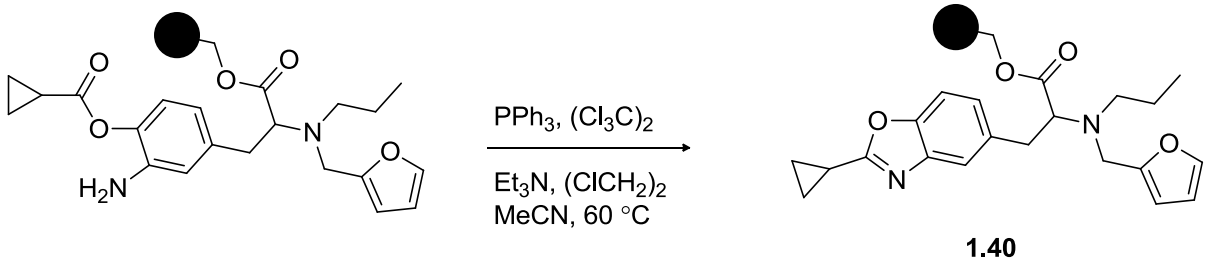
The need for mild, neutral reaction conditions during the solid phase synthesis of a benzoxazole library prompted Wang and Hauske[120] to use the Mitsunobu reaction[121] as their method of cyclodehydration (Scheme 1.8). Excess triphenylphosphine and diethyl azodicarboxylate (DEAD) were stirred in tetrahydrofuran at room temperature to furnish the benzoxazole compounds **1.39** in good yields. Marsden *et al.*[122] also found that the use of the Mitsunobu reaction, with added triethylamine and heating to 50 °C, facilitated the synthesis of their α-silylalkylbenzoxazole without degradation of the product as was the case when other methods were used. More examples of the use of this reaction will be dealt with later in this document.



1.39

Scheme 1.8 Example of the solid-phase synthesis of benzoxazoles using the Mitsunobu reaction to perform the cyclodehydration.

Due to synthetic constraints and normal benzoxazole forming reactions not working, Beebe *et al.*[123] needed to form the benzoxazole **1.40** from the corresponding ester (see Scheme 1.9). Making use of chemistry developed by Vorbruggen and Krolikiewicz the cyclisation was completed in good yields.[124] This method relies on the *in situ* formation of triphenylphosphine dichloride, from triphenylphosphine and carbon tetrachloride or hexachloroethane, which together with triethylamine in acetonitrile then proceeds to assist with the intramolecular cyclisation. More examples of the use of this method are available for the interested reader.[125, 126]

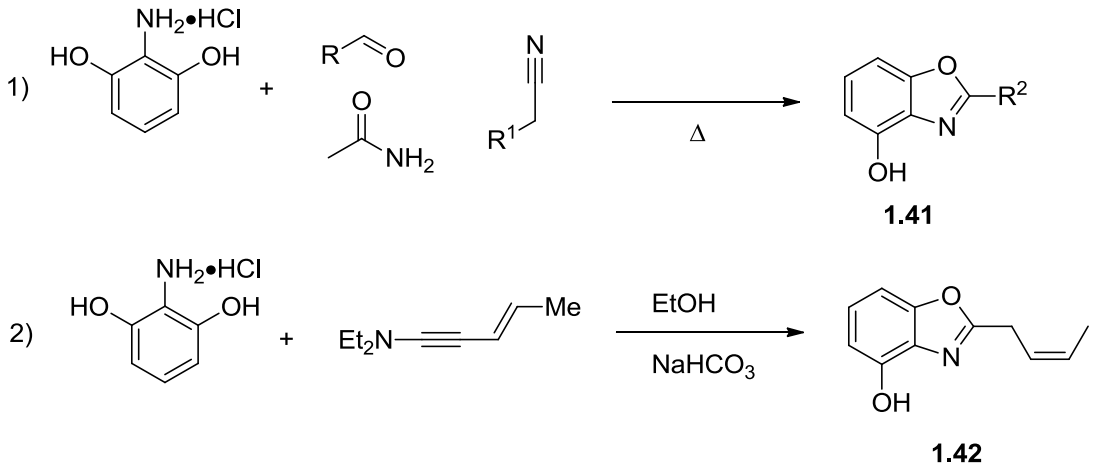


1.40

Scheme 1.9 Example of the synthesis of benzoxazoles using the *in situ* formation of triphenylphosphine dichloride.

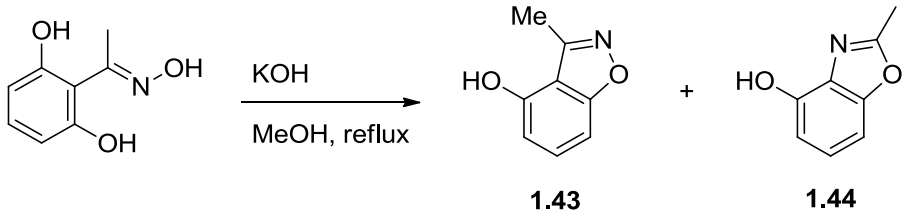
1.1.2.3 Synthesis of 4-hydroxybenzoxazoles

The classical synthesis of 4-hydroxybenzoxazoles **1.41** (Scheme 1.10, reaction 1) made use of the direct condensation of 2-aminoresorcinol hydrochloride with the appropriate acid, amide or cyanide under high temperatures.[73, 74, 127] These compounds were purified by a combination of sublimation, distillation and crystallization. Kormer *et al.*[128] synthesized 2-(2-alkenyl)-4-hydroxybenzoxazoles **1.42** (Scheme 1.10, reaction 2), making use of the direct condensation of 2-aminoresocinol hydrochloride and various alkenynamines at very mild reaction conditions in ethanol. This reaction was also used to synthesise benzoxazoles and other benzazole ring systems.[129] More examples of direct condensation are also available.[130-132]



Scheme 1.10 Synthesis of 4-hydroxybenzoxazole derivatives using direct condensation between 2-aminoresorcinol hydrochloride and various compounds (R = NH_2, OH; R^1 = benzyl, methyl; R^2 = H, methyl, benzyl, ethyl).

During their study on the base-induced transformation of oximes, Crabbe *et al.*[133] found that they could control the outcome of the reaction by changing the ratio of base to starting material (Scheme 1.11). Using 0.5 equivalents of potassium hydroxide in refluxing methanol they found that 2,6-dihydroxyacetophenone was converted 100% to 4-hydroxy-3-methylbenzisoxazole **1.43**. Increasing the base equivalents saw the formation of 4-hydroxy-2-methylbenzoxazole **1.44** and at 12 equivalents the starting material is converted to roughly 83% benzoxazole and the rest to the benzisoxazole isomer. This method was also later used for the synthesis of possible Kv3 channel inhibitors, using excess pyridine to facilitate the ring formation.[134]



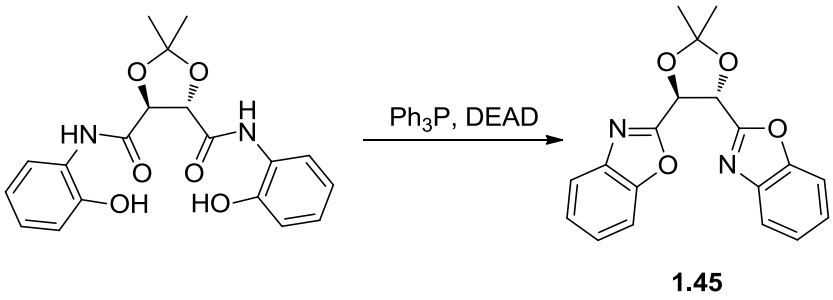
Scheme 1.11 Base-induced formation of 4-hydroxy-2-methylbenzoxazole **1.44** from 2,6-dihydroxyacetophenone.

The use of dehydrating agents to perform the cyclisation of the benzamide precursor to 4-hydroxybenzoxazoles has also been reported. These include $POCl_3$,[135] 4-toluenesulfonic acid[136] and an acetic acid/ trifluoroacetic acid mixture.[137]

1.1.2.4 Introduction of stereochemistry in benzoxazoles

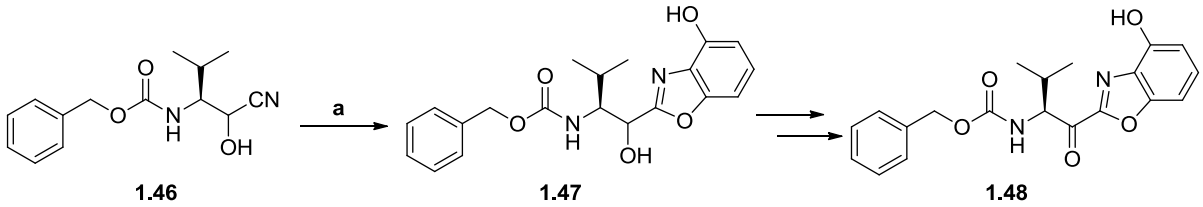
The general synthesis of chiral benzoxazoles usually stem out of the use of chiral starting materials. Therefore this part will only cover some of the methods used to perform the cyclisation reaction. The chiral examples used in section 1.1.1.5 all originated from the reaction of the deprotonated amine on the chiral moiety with 2-chlorobenzoxazole.[47, 48]

Starting from L- and D-tartaric acids Jiao *et al*.[138] synthesised C_2-symmetric enantiomerically pure bisbenzoxazole ligands **1.45**, using the Mitsunobu reaction to perform the cyclisation (Scheme 1.12). These ligands however performed poorly during their subsequent tests and did not induce any stereochemical control. The Mitsunobu reaction was also used by Hou *et al*.[13] with great success in the synthesis of a range of histone deacetylase inhibitors, of which NK-HDAC-1 (see Figure 1.2) was the most promising lead for further investigation.



Scheme 1.12 Ring-closing step in the synthesis of C_2-symmetric bisbenzoxazoles **1.45**, using a Mitsunobu reaction.

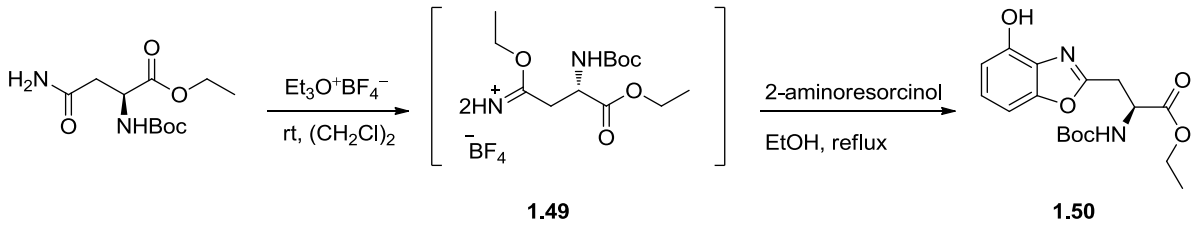
As part of their study towards the synthesis of a library of peptide-based, carboxylic acid containing transition-state inhibitors of Human Neutrophil Elastase (HNE), Sato *et al*.[139] made use of a Pinner condensation to form the 4-hydroxybenzoxazoles **1.47** (step **a**, Scheme 1.13).



Scheme 1.13 Example of the synthesis of a chiral HNE inhibitor **1.48**, making use of a Pinner condensation as the first step. *Reagents and reaction conditions*: (a) (i) HCl, EtOH, $CHCl_3$; (ii) 2,6-dihydroxyaniline, Et_3N, EtOH.

The cyanohydrin **1.46** was converted *in situ* to an imidate ethyl ester, using ethanol and hydrochloric acid, and this was reacted with the substituted 2-aminoresorcinols to form **1.47**. Subsequent synthetic steps led to a library of chiral compounds that were used in the initial activity screening (**1.48**).

Pichota *et al.*[140] also made use of this reaction to synthesise a library of chiral proline-benzoxazole derivatives in their study towards peptide deformylase inhibitors of *Mycobacterium tuberculosis*. For the formation of the imidate ethyl ester they made use of acetyl chloride in ethanol. Zhang *et al.*[141] in their one-pot synthesis of hydroxybenzoxazole-2-aliphatic acid derivatives **1.50** (Scheme 1.14), made use of Meerwein's reagent ($Et_3O^+BF_4^-$) to synthesize imidate ethyl ester tetrafluoroborate salts **1.49** from succinamic acid ethyl ester, malonamic acid ethylester or *N*"-Boc-L-argininate ethyl ester. The imidate salts were reacted with various dihydroxy-anilines and formed the corresponding hydroxybenzoxazoles in good yields and also did not influence the chirality of the *N*"-Boc-L-argininate ethyl ester.



1.49 **1.50**

Scheme 1.14 Example of the use of Meerwein's reagent in the synthesis of chiral hydroxybenzoxazole **1.50**.

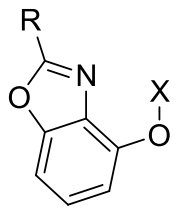
1.2 Conclusion

The aim of this review was to introduce the reader to some of the general aspects of benzoxazole chemistry, with the focus on the coordination chemistry of benzoxazoles as well as the asymmetric synthesis of benzoxazole compounds. Although a lot of work has been performed on these subjects there is still room for further development, especially towards the use of 4-hydroxybenzoxazoles as ligands.

1.3 Objectives of this Study

Asymmetric synthesis is a key area in organic chemistry and has seen an explosion of new technologies over the last three decades. Although there are many excellent asymmetric catalysts available, there still exist structural motifs that have not yet been examined for their

ability to act as asymmetric ligands. In our interest in resorcinarenes, we became aware of such a structural motif, the 4-hydroxybenzoxazole shown in Figure 1.15. This structural motif should be well-suited as a bidentate chiral ligand since it bears the prerequisite features of many known ligands.[142]



X = -P, -H; R = chiral group

Figure 1.15 An example of a chiral benzoxazole

To achieve this, the study would be broken down into four subsections. Data from each subsection would contribute to the synthesis of the final chiral ligands.

Part 1: There is not a lot of data available on 4-hydroxybenzoxazoles and their use as ligands in coordination chemistry. Using achiral derivatives, the suitability of these molecules as ligands will be investigated by forming coordination complexes with various transition metals and testing them with common C−C forming reactions (Heck, Suzuki, etc.).

Part 2: Running parallel with Part 1 would be the establishment of a methodology to functionalise the phenol moiety of the achiral 4-hydroxybenzoxazoles with P(III) functional groups. The suitability of these molecules as ligands will be again investigated by forming coordination complexes with various transition metals and if successful, testing them in common C−C forming reactions (Heck, Suzuki, etc.).

Part 3: This part of the study would wholly be focused on the development of a method to synthesise chiral derivatives of the 4-hydroxybenzoxazoles, via the introduction of amino acids. These compounds would also be tested for antimicrobial activity as part of the broadening of the scope of the hydroxybenzoxazole motif.

Part 4: If satisfactory results were obtained in the three previous sections, the chiral derivatives would be transformed to the final products as seen in Figure 1.15 and tested in various reactions (palladium-catalysed allylic alkylation, iridium-catalysed hydrogenation etc.) to see if asymmetry could be introduced to the substrates.

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CHAPTER 2

Benzoxazole Synthesis

2.1 Introduction

As mentioned in the previous chapter there are a wide range of methods available to synthesize the benzoxazole scaffold.[1-3] For this study a small library of 4-hydroxybenzoxazoles were synthesized (Figure 2.1) with different R-groups on the 2-position (R = H, Me, Ph, Bn, CF_3), using different methods. By changing the R-groups on the molecules it was envisaged that these could exhibit different electronic and steric interactions in the further reactions and functionalisation of the 4-hydroxybenzoxazoles.

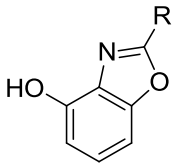
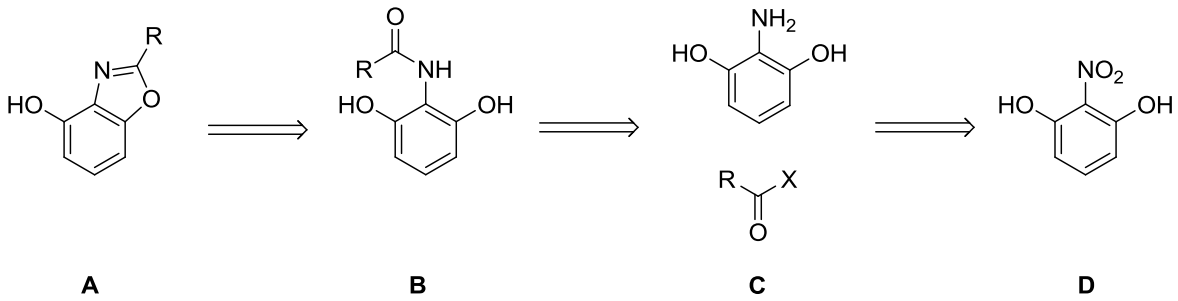


Figure 2.1 The target 4-hydroxybenzoxazoles library (R = H, alkyl, aryl)

Most of the compounds in this study have been synthesised in the literature by condensing 2-aminoresorcinol hydrochloride and carboxylic acid derivatives under acidic conditions,[4-8] or by the base induced transformation of 2,6-dihydroxyacetophenone oxime to form 2-methylbenzoxazole (R=Me, see Figure 2.1).[9] A general retrosynthesis for this work can be viewed in Scheme 2.1. It was envisaged to perform the synthesis as a two-step process, in this way each step could be carefully optimised to obtain the best yields and possibly establish methods to synthesize the chiral benzoxazoles (Chapter 5) later in the study.

For this synthesis it was envisaged that **A** could be formed by a thermal cyclodehydration of amide **B** under acidic conditions. **B** in turn could arise from the acylation of the known amine **C**, making use of carboxylic acids or derivatives. **C** could be synthesized by reduction of 2-nitroresorcinol (**D**), which in turn can be procured by the electrophilic aromatic nitration of resorcinol.

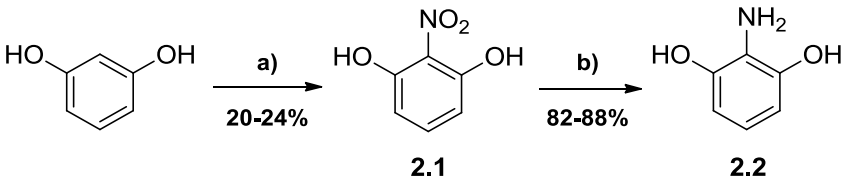


Scheme 2.1 Retrosynthesis for the synthesis of achiral benzoxazole ligands (R = functional group such as CH_3, H, CF_3, phenyl, benzyl; X = -OH, -Cl, RCO_2-)

Part of this work was focused on the characterisation of these compounds, since quite a few of them have only been partially characterised. Efforts to look at their solid state structures with the help of X-ray diffraction studies was also undertaken as part of the characterisation of these compounds.

2.2 Synthesis of functionalized amides

The first step of the synthesis (Scheme 2.2) was that of the nitroresorcinol **2.1**, using an adapted procedure by Schraffarth.[10] This ingenious method makes use of sulfonic acid groups to block the most accessible 4- and 6-positions on the resorcinol, forcing another substituent (-NO_2 in this case) into a more hindered but reactive position. The sulfonate groups can then be removed leaving the desired product. The resorcinol, in concentrated sulfuric acid, was treated with a mixture of concentrated nitric (65% v/v) and sulfuric acid. Steam distillation of the mixture afforded an orange solid, which was crystallised in a water/ethanol mixture to yield large orange needles in a reproducible yield of 20-24%, as reported by Schraffarth.[10]



Scheme 2.2 Synthesis of aminoresorcinol **2.2**. *Reagents and reaction conditions*: a) i) H_2SO_4, rt ii) HNO_3, H_2SO_4, 0 °C→rt. b) H_2, 10 mol% Pd/C, MeOH, rt.

The nitroresorcinol was then reduced to amine **2.2** by warming a mixture of hydrazine hydrate, 10 mol% palladium on carbon (Pd/C, 10% w/w) in ethanol to reflux.[11] After two

hours the reaction was complete according to thin layer chromatographic analysis, with some minor by-products also visible. Work-up and purification using column chromatography and recrystallization from a mixture of ethyl acetate, petroleum ether and methanol returned **2.2** in a low yield of 45% as a fine brown solid. The amine appeared to be very unstable when heated and also when in solution for long periods, thus troubling purification.

The reduction was repeated using 10 mol% palladium on carbon (10%) and hydrogen gas (H_2) in ethanol at ambient temperature, revealing a brown product and no other products according to the thin layer chromatographic analysis, which facilitated the purification of the amine. Repeating the reaction with methanol (Scheme 2.2) returned an even cleaner product, a light brown solid, that eased purification and it was decided to use methanol as the preferred solvent for hydrogenations. Although reaction yields were almost quantitative, purification using column chromatography and especially recrystallization was troublesome. It was found that the cleanest product was procured by triturating the amine **2.2** from a warm, concentrated ethyl acetate solution using hexane, resulting in yields of 82-88% of the fine light brown amine crystals.

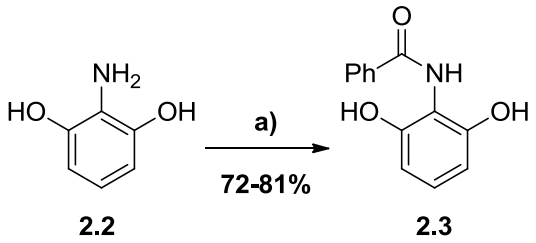
Upon scale up of the reaction large quantities of palladium on carbon were used to facilitate the reduction. Reducing the amount of palladium on carbon from 10 to 2.5 mol% returned very good results, with a slight increase in reaction time from four to six hours.

It was decided to also look at more environmentally friendly routes towards the synthesis of **2.1** and **2.2**. The synthesis of the nitro **2.1** was approached using a method from Badgujar *et al*.[12] Sodium nitrite ($NaNO_2$), tetrahydrofuran, resorcinol and silica was irradiated in a microwave reactor, but no product was formed after several attempts. The reduction of the nitro **2.1** to amine **2.2** was attempted using a synthetic method from Ausin *et al.*[13] **2.1** was reacted with sodium dithionite in an ethanol/water (2.9:1 v/v) mixture. The product **2.2** was returned in a yield of 70%, but the combination of a messy work-up and purification swung the vote back to using the cleaner Pd/C reduction step.

With the amine in hand, attention was turned to synthesize the functionalised amides. The chemistry of these types of reactions is very well known and the use of acylating agents and carbodiimide coupling reagents was investigated for the formation of the amide bonds.[14-16]

2.2.1 Acyl chloride chemistry

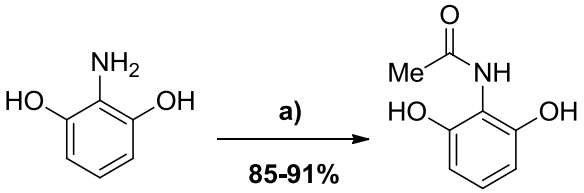
To synthesize the amide **2.3** (Scheme 2.3), a test reaction based on a procedure by Tojo *et. al.*[17] were performed.



2.2 **2.3**

Scheme 2.3 Synthesis of the phenylamide **2.3**. *Reagents and reaction conditions*: a) i) Et_3N (5 equiv.), THF, 0 °C. ii) PhC(O)Cl (1.03 equiv.), 0 °C→rt.

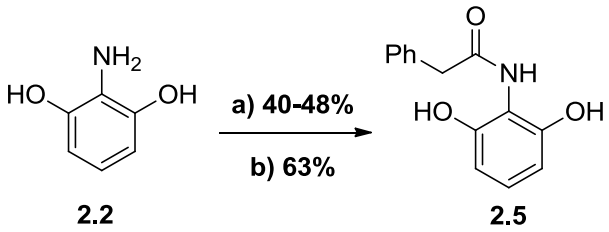
The aminoresorcinol **2.2** was dissolved in anhydrous tetrahydrofuran and the reaction mixture cooled to 0 °C. To this mixture was added five equivalents of triethylamine and this was stirred for 15 minutes to equilibrate at the temperature. 1.03 equivalents of benzoyl chloride were slowly added to the mixture and the yellow emulsion was allowed to warm to room temperature and left to stir overnight. The reaction was then treated with a 5M potassium hydroxide solution for two hours to hydrolyse any ester groups that may have formed and after acidic aqueous work-up, thin layer chromatographic analysis of the reaction revealed only one spot. The product was purified using column chromatography to yield the phenylamide **2.3** in 72% yield. Repeating the reaction on larger scale (1.00 g) exhibited reproducible results with isolated yields between 72-81%.



2.2 **2.4**

Scheme 2.4 Synthesis of amide **2.4**. *Reagents and reaction conditions*: a) i) Et_3N (5 equiv.), THF, 0 °C. ii) $CH_3C(O)Cl$ (1.03 equiv.), 0 °C→rt.

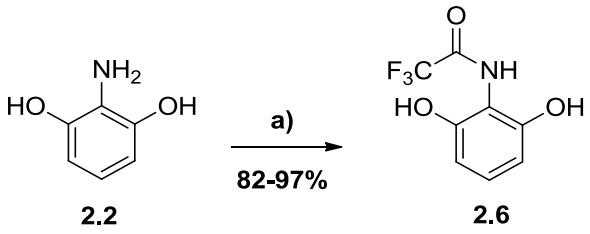
The acylation method was also applied in turn to acetyl chloride and 2-phenylacetyl chloride (generated *in situ* from phenylacetic acid, oxalyl chloride and *N,N*-dimethylformamide, using a procedure by Buttner *et al*.[18]) to return the amides **2.4** and **2.5** in reproducible yields of 85-91% and 40-48% respectively (Scheme 2.4 and Scheme 2.5) after column chromatography. When 2-phenylacetyl chloride was generated from thionyl chloride the yield of amide **2.5** was increased to 63% after column chromatography.



2.2 **2.5**

Scheme 2.5 Synthesis of amide **2.5** using two different methods. *Reagents and reaction conditions*: a) i) BnCOOH (1.03 equiv), $(COCl)_2$ (excess), DMF, DCM, 0 °C→rt. ii) **2.2** (1 equiv.), Et_3N (5 equiv.), THF, 0 °C. iii) BnC(O)Cl (1.03 equiv.), 0 °C→rt. b) i) BnCOOH (1.05 equiv), $SOCl_2$ (excess), DCM, 0 °C→rt. ii) **2.2** (1 equiv.), Et_3N (6 equiv.), THF, 0 °C. iii) BnC(O)Cl (1.05 equiv.), DCM, 0 °C→rt.

For the synthesis of the trifluoroacetamide **2.6** (Scheme 2.6), a different method had to be used. Trifluoroacetyl chloride is a gas and thus could not be generated safely *in situ*. Therefore, trifluoroacetic acid anhydride and triethylamine were allowed to react with amine **2.2** in an analogous way for the synthesis of the other amides, yielding the trifluoroacetamide **2.6** in 23% yield and returning the amine **2.2** as the rest of the material. The product was very acid labile, which caused problems with the work-up. Changing the base to pyridine and following a procedure of Sun *et al.*[14] resulted in the formation of **2.6** in 82% yield after purification by column chromatography. Slower addition of the anhydride, coupled with longer reaction times returned yields of up to 97%.



2.2 **2.6**

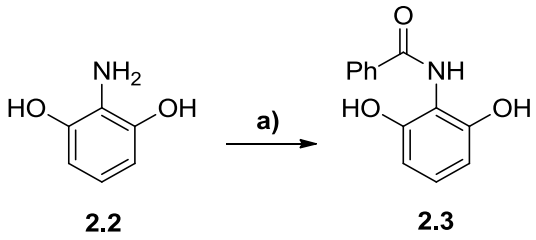
Scheme 2.6 Synthesis of amide **2.6**. *Reagents and reaction conditions*: a) i) C_6H_5N (2 equiv.), THF, 0 °C. ii) $(CF_3CO)_2O$ (1.3 equiv.), 0 °C→rt.

To perform the next step of the synthesis the material was sufficiently pure after column chromatography, but for characterisation recrystallization of the acylated products was needed to remove very small impurities. Initial attempts at recrystallization of the products met with the same problems as amine **2.2**. This was solved by using the same triturating procedure to clean up **2.2**, to furnish very clean products. All the compounds were

characterised by melting point, FT-IR, high resolution mass and NMR (^{1}H, ^{13}C and ^{19}F for **2.6**) spectroscopy and compared with literature values where possible.

2.2.2 Carbodiimide coupling reagents

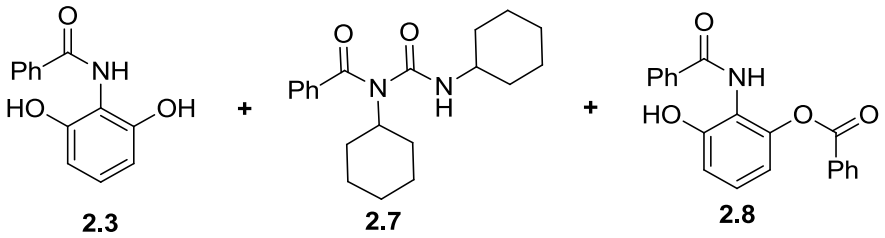
It was decided to also investigate the synthesis of the functional amides using carbodiimide coupling reagents *N,N'*-dicyclohexylcarbodiimide (DCC) and *N,N'*-diisopropylcarbodiimide (DIC), by means of an adapted method from Tiefenbacher *et al.*[19] To achieve this, amine **2.2** was reacted with benzoic acid and the carbodiimide coupling reagents in equimolar quantities to form phenylamide **2.3** as a model reaction (Scheme 2.7).



2.2 **2.3**

Scheme 2.7 Proposed synthesis of the phenylamide **2.3**. *Reagents and reaction conditions*: a) i) PhCOOH, DCC, solvent, additive, 0 °C. ii) **2**, 0 °C→rt.

DCC was added to a suspension of amine **2.2** and benzoic acid in dry dichloromethane at 0 °C and stirred for 15 minutes, after which it was allowed to warm to room temperature and stirred overnight. Thin layer chromatographic analysis revealed the disappearance of the benzoic acid and the formation of several new compounds, but large amounts of the amine was still visible. The reaction was worked-up and due to the close proximity of the three products it could only be partially purified using column chromatography. ^{1}H and ^{13}C NMR spectroscopic analysis of the product mixtures revealed the formation of the acylated urea **2.7** (32%), the di-acylated product **2.8** (48%) and the phenylamide **2.3** in less than 8% yield. When the reaction was repeated using acetonitrile or tetrahydrofuran more of product **2.3** was seen, probably due to the higher solubility of the amine **2.2** in these solvents, but there was still a high percentage of by-products in the reaction (Figure 2.2).



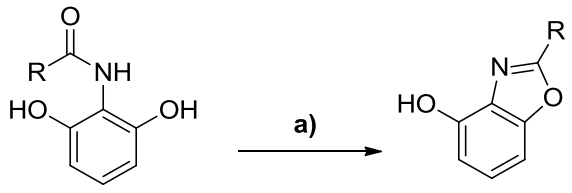
2.3 **2.7** **2.8**

Figure 2.2 Products formed in the coupling reaction of amine **2.2** with benzoic acid using coupling reagents.

With the addition of one equivalent of 1-hydroxybenzotriazole (HOBt) to the reaction less of the acylated urea **2.7** was formed with an increase in the formation of **2.3** and **2.8** and changing the coupling reagent to DIC (with HOBt) an almost equal quantity of **2.3** and **2.8** was formed. Due to the low yields and difficulty in purification that was experienced in the course of this model study, it was decided to not pursue the optimisation of these reactions as a means of synthesising the amides.

2.3 Synthesis of the benzoxazoles

The formation of benzoxazoles from *N*-(2-hydroxyphenyl) carboxamides is usually accomplished by an acid-catalysed cyclodehydration at high temperatures.[1-3] Employing a procedure from Buttner *et al.*[18] a catalytic quantity of *p*-toluenesulfonic acid monohydrate (PTSA, 10 mol%) and amide **2.4** was warmed to reflux in xylenes as a test reaction (see Scheme 2.8). After two and a half hours the reaction was complete according to thin layer chromatographic analysis and the product was purified by an aqueous work-up. ^{1}H NMR spectroscopic analysis of the crude material revealed the formation of the desired product. The reaction was repeated with 15 mol% PTSA on a larger scale, returning the methylbenzoxazole **2.10** in 89% yield after column chromatography.



2.3-2.6 **2.9-2.12**

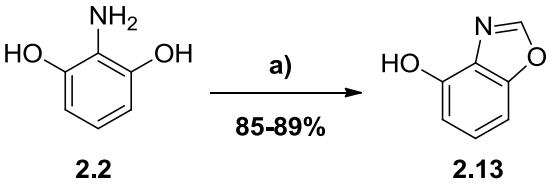
2.3→**2.9** R = Ph (82%)
2.4→**2.10** R = Me (89%)
2.5→**2.11** R = CH_2Ph (85%)
2.6→**2.12** R = CF_3 (82%)

Scheme 2.8 Synthesis of benzoxazoles **2.9-2.12** through cyclodehydration. *Reagents and reaction conditions*: a) i) PPTSA (cat.), toluene, reflux.

The procedure was applied to amide **2.3** (R=Ph) and after four hours the reaction was worked up and purified by column chromatography, returning the phenylbenzoxazole **2.9** in 53% yield and recovered amide **2.3**. The recovered starting material was used in a repeat of the reaction, leaving to reflux overnight. Thin layer chromatographic analysis revealed only a small amount of product formation and some degradation products that could not be retrieved. Using a mixture of 1,4-dioxane and xylene (1:1 v/v), to obtain better solubility of the amide **2.3**, only resulted in longer reaction times (54 hours) and also more degradation as the reaction progressed. This was also observed for the synthesis of benzyl-hydroxybenzoxazole **2.11** (R=Bn) from amide **2.5**. Using dry toluene as solvent also increased the reaction time, but when this was used in conjunction with a milder Bronsted acid, pyridinium *p*-toluenesulfonate (PPTSA), cleaner reactions with less degradation were observed. Using this method 4-hydroxybenzoxazoles **2.9**-**2.11** could be synthesized consistently with yields of >80% after purification with column chromatography and recrystallization from their various solvents.

For the synthesis of the trifluoromethylbenzoxazole **2.12** (Scheme 2.8) it was deemed necessary to use the milder Bronsted acid, since **2.6** was more sensitive to stronger acids, as seen during its work-up. Amide **2.6** was warmed to reflux with PPTSA in toluene and after 22 hours the reaction was stopped and worked-up. Following purification with column chromatography a light yellow oil was recovered. After drying on a high vacuum pump a yield of only 23% for **2.12** was returned. The thin layer chromatograph analysis of the aqueous layers revealed no product and flushing of the column also produced no more products. While experimenting with the work-up procedure it was found that it was better to subject the reaction mixture directly to column chromatography for purification, due to the product possibly being susceptible to hydrolysis, and to use high vacuum drying to a minimum. Attempts to purify the yellow oil further were not successful, but the serendipitous addition of a small amount of hexane to the oily residue resulted in the formation of fine white crystals after cooling on an ice bath. These were however too fine to isolate. Repeating the procedure, and cooling in a fridge at −20 °C, produced larger white crystals which were collected after a few days. The recrystallization process was fine-tuned to yield trifluoromethylbenzoxazole **2.12** in 82%.

To complement the small library, 4-hydroxybenzoxazole **2.13** (Scheme 2.9), was synthesized by the direct cyclisation reaction of 2-aminoresorcinol **2.2** and trimethyl orthoformate with PTSA in refluxing xylenes or PPTSA in toluene in high isolated yields (85-89%).



2.2 **2.13**

Scheme 2.9 Synthesis of benzoxazole **2.13** through direct cyclisation. *Reagents and reaction conditions*: a) i) $CH(OMe)_3$, PPTSA (cat.), toluene, reflux.

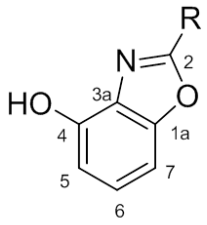
The benzoxazoles derivatives **2.9**-**2.13** were characterised by melting point, FT-IR, high resolution mass andNMR (^{1}H, ^{13}C and ^{19}F for **2.12**) spectroscopy and compared with literature values where possible.

Due to various reports in the literature on the direct synthesis of benzoxazoles from aminophenols and acids or acid chlorides,[20-22] attempts were also made at performing the cyclodehydration with a microwave reactor. However in our hands it was shown that large amounts of degradation occurred and that higher yielding products were formed when using conventional heating. These reactions exhibited quite a marked difference in reaction times as the steric bulk in the 2-position increased. 4-Hydroxybenzoxazoles **2.10** and **2.13** were complete in less than 4 hours, whereas **2.9** would take up to seven days to complete the cyclisation, under exactly the same conditions as the synthesis of the other compounds. The compounds also exhibited quite different solubility characteristics. 4-Hydroxybenzoxazoles **2.9**, **2.10** and **2.12** were soluble in polar organic solvents, showing slight solubility in diethyl ether and toluene (at high dilution) and were insoluble in all the alkanes. Benzoxazole **2.11** and **2.13** however revealed partial solubility in most organic solvents and were only soluble in polar and very polar solvents (most of the alcohols, tetrahydrofuran, *N,N*-dimethylformamide etc.).

2.3.1 Characterisation

It was decided to have a close look at the NMR (^{1}H and ^{13}C) and FT-IR spectroscopic data of the compounds **2.9**-**2.13** to facilitate the studies that would be performed later on them. The most important data can be viewed in Table 2.1.

Table 2.1 Important characterisation data (^{1}H, ^{13}C NMR and FT-IR spectroscopy) of benzoxazoles **2.9**-**2.13**. NMR and IR data reported in ppm and cm^{-1} respectively.



	2.9 (Ph)[b]	2.10 (Me)[b]	2.11 (Bn)[c]	2.12 (CF_3)[b]	2.13 (H)[c]
			^{1}H NMR[a]		
R	7.44-7.56 (3H, m, Ar-H) 8.14-8.24 (2H, m, Ar-H)	2.71 (3H, s, −CH_3)	4.29 (2H, s, –CH_2–) 7.25–7.39 (5H, m, Ar–H)	-	8.55 (1H, s, =C–H)
OH	8.40	10.28	10.20	7.72	10.33
5	6.92 (dd, J = 8.1, 0.9 Hz)	6.89 (dd, J = 8.1, 0.9 Hz)	6.70 (dd, J = 8.0, 1.0 Hz)	6.98 (dd, J = 8.2, 0.8 Hz)	6.77 (dd, J = 7.9, 1.0 Hz)
6	7.26 (t, J = 8.1 Hz)	7.22 (t, J = 8.1 Hz)	7.12 (t, J = 8.1 Hz)	7.41 (t, J = 8.3 Hz)	7.20 (t, J = 8.0 Hz)
7	7.15 (dd, J = 8.2, 0.9 Hz)	7.04 (dd, J = 8.2, 0.9 Hz)	7.04 (dd, J = 8.2, 0.9 Hz)	7.19 (dd, J = 8.4, 0.8 Hz)	7.14 (dd, J = 8.2, 1.0 Hz)
			^{13}C NMR[a]		
2	161.9	163.7	163.0	150.4 (q, J_{C-F} = 44.0 Hz)	152.1
			FT-IR[d]		
C=N	1619	1627	1632	1622	1628

[a]100 MHz [b]$CDCl_3$ [c]d_6-DMSO [d]ATR

From the ^{1}H NMR spectroscopic data it was observed that all the compounds exhibited the same generic splitting pattern in the aromatic area, consisting of two doublet of doublets (for H-5 and -7) and a triplet (for H-6). In deuterated chloroform the phenol signal could be observed as a very broad singlet, possibly due to the large amount of hydrogen bonding that was occurring between the molecules. With deuterated dimethylsulfoxide a very sharp signal around 10 ppm was visualised due to the compounds forming hydrogen bonds to the solvent and thus shifting more upfield.[23]

It was envisaged that coordination of these compounds to transition metals could be verified by not only the shift of the ν(C=N) band in FT-IR spectroscopy, but also by the shift of the carbon (C-2, see Table 2.1 for numbering) in the ^{13}C NMR spectroscopy. An interesting correlation was observed from these measurements. Benzoxazole **2.13** revealed a shift of

152.1 ppm for C-2, the electron donating R-groups (Me, Ph, Bn) all revealed downfiled shifts around 160-163 ppm and the electron withdrawing CF_3 shifted the C-2 carbon signal to 150.4 ppm, seen as a quartet due to C-F coupling.

FT-IR spectroscopy of benzoxazoles **2.10**-**2.13** revealed very broad bands in the region of 3500-2500 cm^{-1} due to the overlapping of the C-H aromatic stretch and O-H phenol stretch vibrations. It could also be deduced that there is a high degree of hydrogen bonding present in the solid state, a characteristic that was also observed in the ^1H NMR spectroscopic data. Benzoxazole **2.9** displayed some clear differences in the bands that could be associated with the C-H aromatic stretch and O-H phenol stretch vibrations, due to the high degree of conjugation that is found throughout the molecule. Making a clear and definite assignment of the C=N stretch band of these compounds were not as trivial, due to the overlapping of the aromatic C=C and C=N stretching frequencies. It was decided to study the changes in the whole area of 1650-1550 cm^{-1} in all of the further work on these compounds, using the values in Table 2.1 as a reference point. In a similar fashion the C-O stretching frequencies in the area of 1300-1000 cm^{-1} will also be taken into account in further work.

2.3.2 Structural studies

A search* of the CCDC (Cambridge Crystallographic Data Centre) did not produce any structures for the 4-hydroxybenzoxazole compounds and it was decided to investigate using X-ray diffraction crystallography. Crystallisations of these ligands were set-up in various solvents, of which X-ray quality crystals could be isolated for benzoxazoles **2.10** and **2.11**.

*2.3.2.1 Single crystal structure of benzoxazole **2.10***

Suitable single crystals of methylbenzoxazole **2.10** were grown by slow diffusion of petroleum ether into a concentrated dichloromethane solution of the benzoxazole with subsequent evaporation at room temperature. **2.10** crystallised in the triclinic space group *P*-1, with two molecules of **2.10** in the asymmetric unit (marked as A and B). Figure 2.3 displays a perspective view of the asymmetric unit of **2.10**, together with the labelling scheme used in the structural refinement.

* Performed on 05/08/2011 with CSD version 5.32 (Aug 2011 updated)

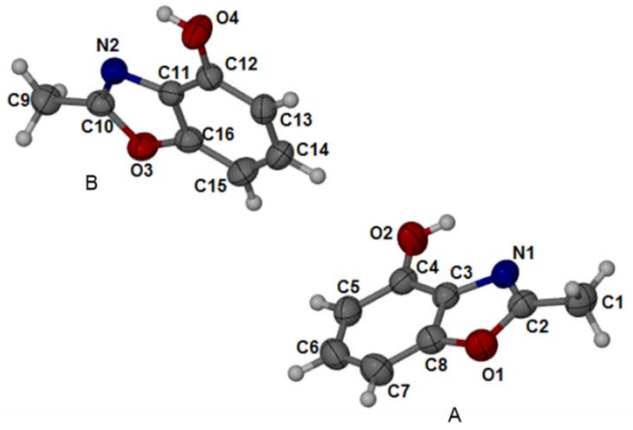


Figure 2.3 Molecular structure of benzoxazole **2.10** with the labeling scheme. All non-hydrogen atoms are drawn with displacement ellipsoids at 50 % probability.

Each of the molecules are almost completely planar (r.m.s. deviation = 0.0149 Å for A and 0.0098 Å for B) and the dihedral angle between the least squares mean planes, passing through molecules A and B, form a slightly distorted right angle [88.10(5)°] with respect to one another.

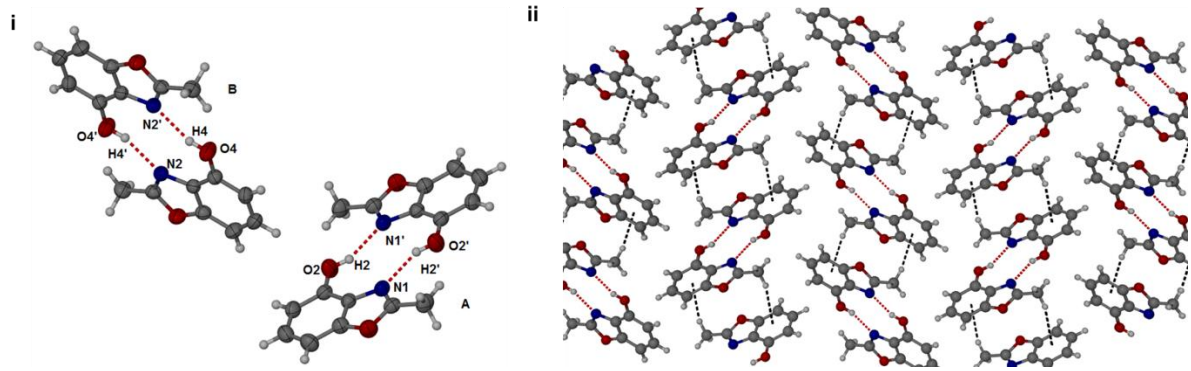


Figure 2.4 Hydrogen bonding in the structure of benzoxazole **2.10**: i) Showing the individual molecules viewed down the *a* axis, with displacement ellipsoids drawn at 50 % probability; ii) Molecular packing viewed along the *a* axis, revealing the zigzag pattern. Molecules are shown in the ball-and-stick representation. Hydrogen bonds are represented as red dashed lines and C-H···π interactions as black dashed lines.

Furthermore these distinct molecules are involved in intermolecular hydrogen bonds (O-H···N, see Table 2.2 and Figure 2.4) that are centro-symmetrically related. The hydrogen bonded ring forms a $R^2_2(10)$ motif.[24] The individual molecules also take part in intermolecular C-H···π interactions with an centro-symmetrically related molecule [C1···centroid of 6-

membered ring (C3-C8) of benzoxazole A = 3.792(4) Å and C9···centroid of 6-membered ring (C11-C16) of benzoxazole B = 3.767(4) Å]. The result of this is the formation of zigzag patterns along two directions. Close contacts interactions also stabilise the two different motifs together, thus forming a network of integrated molecular structures.

Table 2.2 Hydrogen bond geometry for benzoxazole **2.10** (Å, °)

D-H···*A*	**D-H**	**H···*A***	**D···*A***	**<(DH*A*)**
O2-H2···N1^{i}	0.93(2)	1.90(2)	2.774(2)	157(2)
O4-H4···N2^{ii}	0.94(2)	1.89(2)	2.756(2)	153(2)

Symmetry codes: (i) -x+2, -y+1, -z+1; (ii) -x, -y+2, -z

*2.3.2.2 Single crystal structure of benzoxazole **2.11***

Suitable single crystals of benzylbenzoxazole **2.11** were grown by slow evaporation from a concentrated methanolic solution at room temperature. **2.11** crystallised in the triclinic space group *P*-1, with one molecule in the asymmetric unit and no solvent in the crystal structure. Figure 2.5 shows a perspective view of the crystal structure of **2.11**, together with the labelling scheme used in the structural analysis.

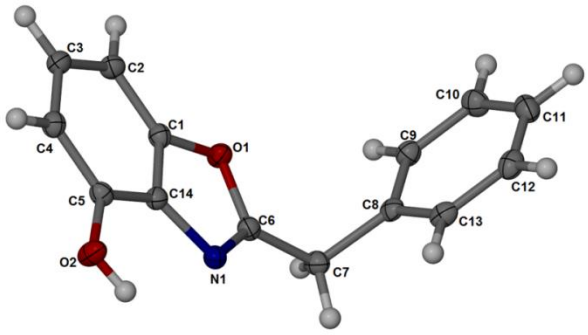


Figure 2.5 Molecular structure of benzoxazole **2.11** with the labeling scheme. All non-hydrogen atoms are drawn with displacement ellipsoids at 50 % probability.

The crystal structure of **2.11** contains intermolecular hydrogen bonds (O-H···N, see Table 2.3 and Figure 2.6) with a centro-symmetrically related molecule, forming a hydrogen bonded ring motif $R^2_2(10)$.[24] Furthermore C-H···π interactions (C3···centroid of adjacent benzyl ring = 3.757(2) Å and C11···centroid of adjacent 6-membered ring of benzoxazole = 3.6998(19) Å) connect the molecules in a head to tail arrangement, making a 1D bi-directional chain down the *c* axis (001). The dihedral angle between the least squares mean

planes of the benzoxazole ring and that of the phenyl ring (C8-C9-C10-C11-C12-C13) is 78.26(4)°.

Table 2.3 Hydrogen bond geometry for benzoxazole **2.11** (Å, °)

D-H···*A*	**D-H**	**H···*A***	**D···*A***	**<(DH*A*)**
O2-H2···N1^{i}	0.96(2)	1.85(2)	2.7549(18)	155(2)

Symmetry codes: (i) 1-x, -y, 1-z

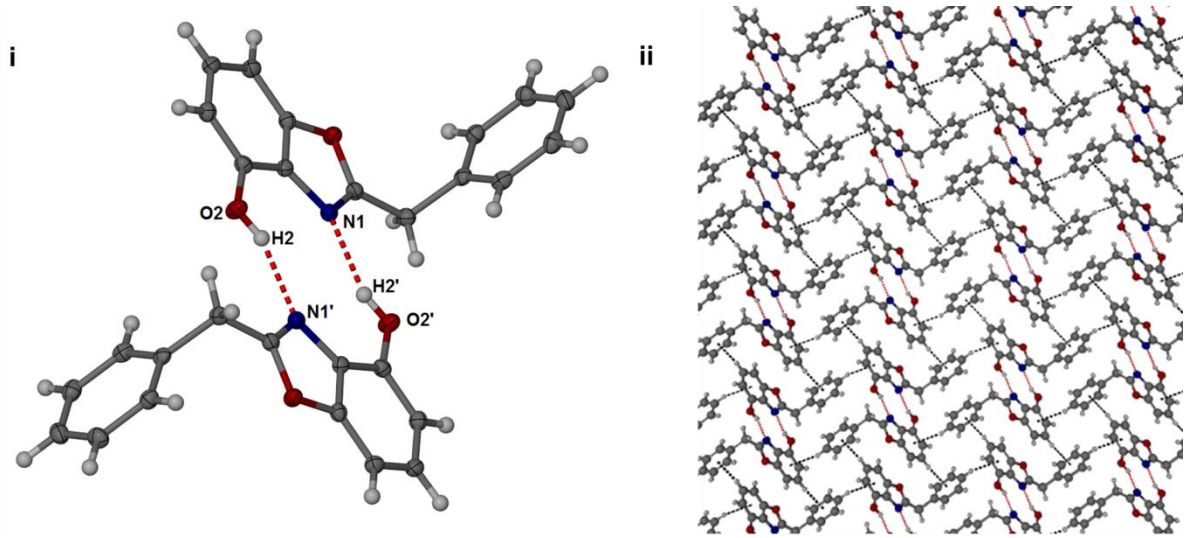


Figure 2.6 Hydrogen bonding in the structure of benzoxazole **2.11**: i) Showing the individual molecules viewed down the *a* axis, with displacement ellipsoids drawn at 50 % probability; ii) Molecular packing viewed along the *a* axis. Molecules are shown in the ball-and-stick representation. Hydrogen bonds are represented as red dashed lines and C-H···π interactions as black dashed lines.

Some of the corresponding bond lengths for the compounds can be seen in Table 2.4, indicating small differences between the two different compounds.

Table 2.4 Selected bond lengths (Å) for compounds **2.10** and **2.11**. Numbering can be seen in Figure 2.3 and Figure 2.5 respectively.

2.10		**2.11**	
N1-C2	1.3006(19)	N1-C6	1.2983(17)
O1-C2	1.3637(18)	O1-C6	1.3656(17)
O2-C4	1.3553(19)	O2-C5	1.3595(17)

With these molecules in hand attention was turned to studying their complexation behaviour by the synthesis and characterisation of their coordination compounds with transition metals.

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CHAPTER 3

Coordination Chemistry

3.1 Introduction

With the benzoxazole ligands in hand attention was turned to investigating the coordination chemistry of the compounds, especially focusing on the structural aspects of the coordination chemistry. From examination of the literature it was clear that 4-hydroxybenzoxazoles have not commonly been used as ligands for transition metals and that very little structural evidence for these compounds could be found.[1-6] Using the available information from related benzoxazole and heterocyclic systems,[7-12] it was envisaged that three possible coordination motifs were possible (Figure 3.1).

Motif I (Figure 3.1 **I**): The formation of the first, and simplest motif, relies solely on coordination through the nitrogen of the C=N bond to a metal centre. Depending on the nature of the transition metal, the number of ligands involved in coordination will also differ. This is a very common motif in benzoxazole chemistry and widely reported.[12-17]

Motif II (Figure 3.1 **II**): The second motif is that of a mono-nuclear complex formed by the coordination of two bidentate ligands to the metal centre. This motif depends on the formation of a bond to the metal centre via phenol, as well as the coordination of the nitrogen atom to the metal centre. There is ample evidence to support the formation of six-membered rings from phenol donating groups incorporated on the 2-position of a benzoxazole,[7, 9-11] but no complexes could be found with 4-hydroxybenzoxazole molecules acting in this manner as bidentate ligands. This coordination motif has been reported with 4-hydroxybenzothiazole molecules,[18] as well as with some benzimidazole derivatives.[19] It would thus be interesting to explore the role of the phenol moiety of the 4-hydroxybenzoxazole ligands, in the process forming five-membered rings.

Motif III (Figure 3.1 **III**): The last motif was based on work performed by Crociani *et al*.[8], where coordination compounds were formed with a three-electron donor, like an acyl group, in hydroxyquinoline derivatives thus also further probing at the interaction of the phenol in these systems.

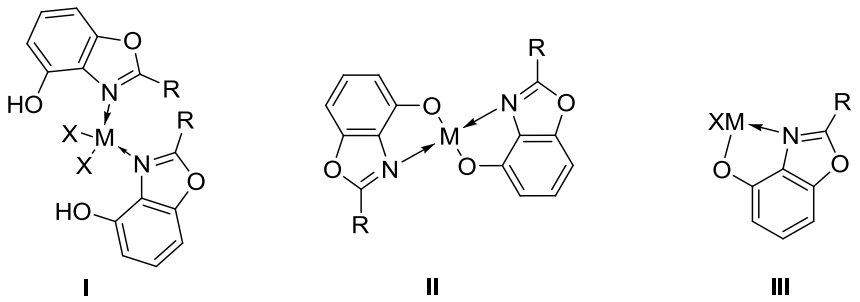


Figure 3.1 Possible coordination motifs from the 4-hydroxybenzoxazole ligands using Group 10 metals as an example (M = metal, X = counter ion for example Cl or allyl, R = aliphatic or aromatic).

It was decided to focus on the synthesis of the coordination compounds using Pd(II) salts, since these complexes could be easily characterised by all the major forms of spectroscopy and could also be tested as catalysts for palladium mediated C-C bond forming reactions (Heck, Suzuki etc.). For the synthesis of the complexes it was decided to use $PdCl_2$, the more soluble and labile $[PdCl_2(MeCN)_2]$ and $Pd(OAc)_2$ as metal sources.

3.2 Synthesis and characterisation of palladium benzoxazole complexes

3.2.1 Attempted metallocycle compound synthesis

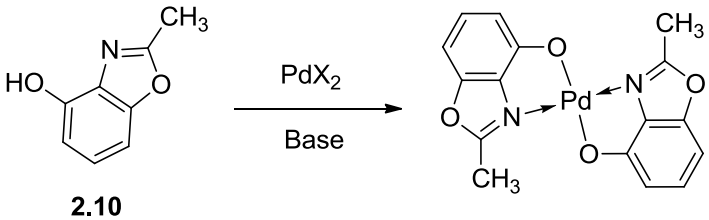
The investigation into the synthesis of the complexes started by using small scale reactions of methylbenzoxazole **2.10** ($R=CH_3$) (0.2-0.4 mmol ligand), $PdCl_2$ and various bases to form the metallocycle compounds (Scheme 3.1).

The first base that was considered for use was triethylamine. An equimolar quantity of triethylamine, metal salt and **2.10** was warmed to reflux in dry dichloromethane for three hours, the mixture quickly turned from light brown to dark brown with the formation of what looked like very fine suspension, after which it was cooled to room temperature and left to stir overnight. The reaction was filtered over Celite®, revealing that the suspension was Pd black [Pd(0), see Scheme 3.1]. ^{1}H NMR spectroscopic analysis of the filtrate displayed a mixture of the base and starting ligand.

When this reaction was performed at room temperature in dichloromethane with $[PdCl_2(MeCN)_2]$ and triethylamine (ligand:metal:base = L:M:B = 2:1:2) no precipitation of Pd(0) occurred. The orange solution was stirred overnight after which it was filtered and the solvent removed. The solid was dissolved in dichloromethane and layered with pentane to

crystallise the product, but as soon as the pentane was introduced to the solution a very fine yellow powder precipitated out of the solution. This powder did not go back in solution and the solvent was removed. ^{1}H NMR spectroscopic analysis of a crude sample revealed starting material, a new product and signals corresponding to triethylamine (or the hydrochloride salt). This reaction was repeated and the solvent was removed. Tetrahydrofuran was added to try and precipitate out the triethylamine hydrochloride salt, if formed in the reaction. Filtration of the sample left an off-white solid and the solvent was removed. ^{1}H NMR spectroscopic analysis of the orange solid in deuterated chloroform corresponded with previous spectra, but after being left for a few hours at room temperature a yellow solid precipitated out of solution. This was also the case when chloroform was added to the rest of the product and a crop of fine yellow solids was recovered. ^{1}H NMR spectroscopic analysis of the solid in deuterated dimethylsulfoxide revealed only the signals that corresponded with the ligand **2.10** (R=CH_3). Efforts to recrystallize the sample from a saturated solution of dimethylformamide, for structural analysis with X-ray diffraction, were not successful. It was decided to look at a different synthetic procedure and come back to this reaction if the reactivity of the compounds was better understood.

The reaction was repeated following a procedure of Samota *et al.*[11] by warming benzoxazole **2.10** (R=CH3) and $PdCl_2$ (L:M = 2:1) in dry ethanol with pyridine as base to reflux. The light brown reaction slowly turned yellow and as it progressed a precipitate was formed. After five hours the heating was stopped, leaving the reaction mixture to stir and gradually cool to room temperature overnight. A tan coloured solid was collected by filtration and washed with ethanol, leaving a clear faint yellow filtrate. ^{1}H NMR spectroscopic analysis of the solid revealed the formation of a compound largely based on pyridine, with some of the starting benzoxazole **2.10** as a minor component in the mixture. It was assumed that the $PdCl_2$ formed a coordination compound with the pyridine and a search of the literature revealed that the unknown compound displayed a good comparison in ^{1}H NMR spectroscopic shifts with dichlorobis(pyridine)palladium,[20] thus returning a yield of 45% (based on the $PdCl_2$, see Scheme 3.1). It became clear that the volume of pyridine added to the reaction was too much for the small scale that was operated on, but more importantly it indicated that pyridine would not be a suitable base to use in future coordination reactions if benzoxazoles were used as ligands, due to the competition that would result for the formation of coordination complexes.



2.10

PdX_2	Base	Solvent	Conditions	Result
$PdCl_2$	Et_3N	DCM	Reflux (3 hours)	SM
$PdCl_2$	pyridine	EtOH	Reflux (5 hours)	$[PdCl_2(pyridine)_2]$ (45%) + SM
$Pd(OAc)_2$	-	EtOH	Reflux (4.5 hours)	SM + unidentified product

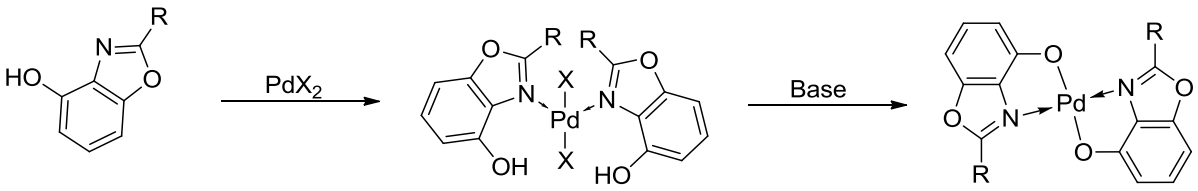
Scheme 3.1 Attempts at the synthesis of metallocycle coordination compounds from methylbenzoxazole **2.10** (SM = starting material = **2.10**).

Another option that was followed was the use of $Pd(OAc)_2$ as the metal salt. It is widely reported that the acetate ion, from metal acetate salts, could act as an *in situ* base that could deprotonate the phenol moiety and drive the formation of the cyclised products, especially utilising alcohols as solvents under reflux temperatures.[18, 21-24] Methylbenzoxazole **2.10** and $Pd(OAc)_2$ (L:M = 2:1) were added together in dry ethanol and the reaction was warmed to reflux.Within a few minutes a precipitate formed. The solution was left for four and a half hours at reflux and the dark brown heterogeneous solution was left to stir overnight at room temperature. The mixture was filtered to leave a large deposit of palladium black and a clear orange solution. The ^1H NMR spectroscopic analysis of the filtrate revealed the starting benzoxazole and the formation of a new product in low yield, but attempts to further purify and identifying the product through crystallization ended in decomposition of the material (Scheme 3.1). Repeating the reaction returned the same result. The reaction was also attempted using benzylbenzoxazole **2.11** to make sure that the result was not due to the ligand, however the same reaction profile was observed and it was decided not to pursue this synthetic route any further.

From the first reactions it became clear that the synthesis of these compounds would not be as trivial as was first anticipated. It was also clear that the combination of a base and high reaction temperatures was not suitable in the synthesis of these compounds and that they are not very stable for extended periods in solution, thus also troubling purification.

To solve the problem a new synthetic route was undertaken. It was decided to first form the di-coordinated compounds (see Scheme 3.2) from $PdCl_2$ and/or $Pd(OAc)_2$ and from these coordination compounds form the metallocycle products using a base to deprotonate the

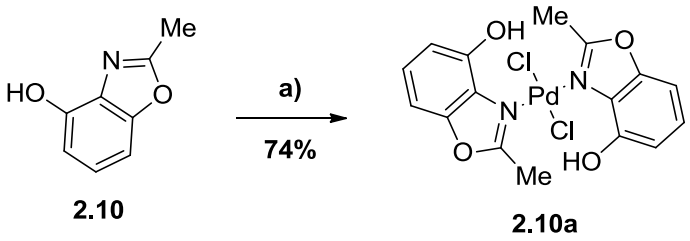
phenol. It was hypothesised that the coordinated compounds would be easier to transform to the metallocycle compound due to the proximity of the reaction centres.



Scheme 3.2 Proposed two-step synthesis of the metallocycle complexes (R = aliphatic, aromatic; X = Cl, OAc).

3.2.2 $PdCl_2$ precursors

$[PdCl_2(MeCN)_2]$ was added to a solution of methylbenzoxazole **2.10** (L:M = 1:1) in dry dichloromethane forming a clear yellow solution (see Scheme 3.3). Within 5-10 minutes a precipitate formed and the reaction was left to stir overnight. A very light yellow (almost greyish) precipitate was collected and washed with dichloromethane and hexane. The solvent of the yellow filtrate was removed and ^{1}H NMR spectroscopic analysis of the filtrate in deuterated chloroform revealed a complicated mixture of products and it was suspected that the product had decomposed. Analysis of the precipitate proved to be a problem due to the extent that it was insoluble in almost all of the organic solvents at room temperature and would only partially dissolve in polar solvents (dimethylsulfoxide, *N,N*-dimethylformamide, acetonitrile, tetrahydrofuran) at low concentrations or at their reflux temperatures. In all the cases the solutions formed by dissolving the lightly coloured precipitate changed from light yellow to reddish solutions. On cooling and standing for a few days small micro-crystals formed, but due to the instability of the compounds and the coordinating nature of the solvents the metal leached out of the crystals forming a black precipitate. This result revealed that the product was most probably the recovered solid and not the filtrate as was assumed in the beginning. This led to some work on maximising the formation of the precipitate as well as the characterisation of the solid.



2.10 **2.10a**

Scheme 3.3 Synthesis of complex **2.10a.** *Reagents and reaction conditions*: a) $[PdCl_2(MeCN)_2]$ (0.5 equiv.), DCM, rt

It was decided to perform the reactions as more concentrated solutions and for a shorter time to discourage the possible decomposition of the products. After stirring for three hours a yellow solid was recovered and thin layer chromatography of the filtrate revealed that almost all of the benzoxazole **2.10** was consumed in the reaction.

^{1}H NMR spectroscopic analysis of the solid in deuterated chloroform did not reveal any usable information due to the low solubility of the product in the solvent. In deuterated dimethylsulfoxide the signals were more distinguishable and from the spectra it was observed what looked like a mixture of starting ligand **2.10** (R=CH_3) and a new product [see Figure 3.2 top spectra, asterisk (*) indicates ligand **2.10**]. What was encouraging was what appeared to be a large shift for the methyl protons (two singlets around 3.00-3.50 ppm compared to a singlet at about 2.60 ppm for ligand **2.10**) as well as the small shifts in the aromatic region pointing to the formation of a new product. The ^{13}C NMR spectrum revealed very weak signals, due to the low solubility, and very little information could be drawn from it. It did however appear as if some shifts had occurred in the signals of the compound. The ^{1}H NMR spectra of the compound in deuterated dimethylsulfoxide was also collected at 50 °C to investigate if better resolution of the signals could be achieved that would give more information on the structure of the compound (see Figure 3.2, bottom spectra). The signals at 50 °C were broader and it appeared as if the signals were merging to form predominately the signals of the starting ligand **2.10**. It appeared as if some ligand dissociation was occurring and it was decided to look at the spectra of all the compounds to see if this was also happening in their cases.

This phenomenon would also explain why the NMR spectra of the reaction of ligand **2.10**, triethylamine and the metal salt, mentioned earlier, returned a spectrum that looked like that of the starting ligand **2.10**. The product that was formed was that of **2.10a** in 74% yield (see Scheme 3.3).

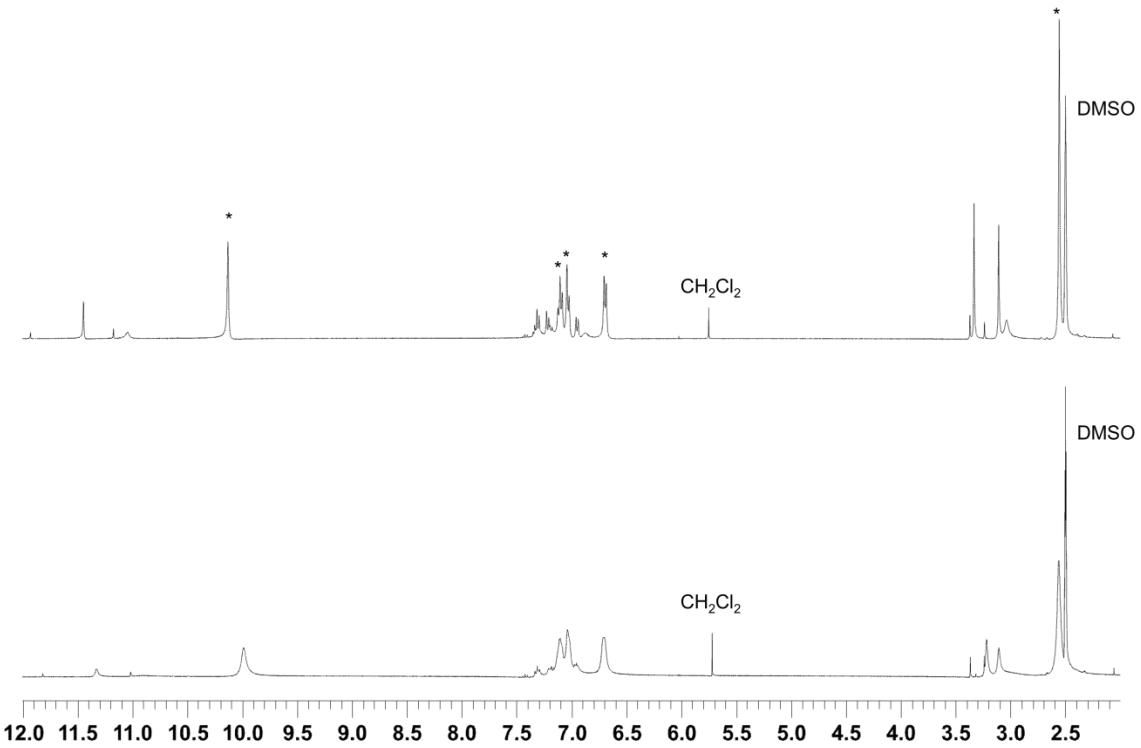


Figure 3.2 ^{1}H NMR spectra of the palladium complex of **2.10a** at room temperature (top) and at 50 °C (bottom) in DMSO-d_6. * indicates the signals that corresponds with ligand **2.10**(R=CH_3**)**.

Due to the thermal instability and relative insolubility of the compound **2.10a** no mass spectrometry data could be gathered to confirm the composition of the product and only a strong peak for the parent ligand **2.10** could be seen, even if a solid phase ASAP probe with APCI (atmospheric pressure chemical ionization) was used. The characterisation data left us in a predicament, since everything pointed to the precipitate being mostly starting material.

FT-IR spectroscopy of the compound however revealed significant changes from the starting benzoxazole (see Table 3.1). In the area from 3300-3000 cm^{-1} a major change could be observed. The ligand **2.10** contains a very broad absorption band with a peak at 3082 cm^{-1} and the newly formed product in turn contained a sharp peak of medium intensity at around 3243 cm^{-1}, covering the –OH stretch and the C-H stretches. The area around 1650-1550 cm^{-1} also contained major changes. The three bands, two weak absorptions at 1627 and 1572 cm^{-1} and the medium absorption at 1608 cm^{-1}, changed to two absorption bands of medium intensity at 1631 and 1591 cm^{-1}. These two represented the ν(C=N) and aromatic ν(C=C) bands respectively. This pointed to coordination through the nitrogen atom of the C=N bond. Taking this and other shifts into account it was postulated that coordination of the Pd occurred through the nitrogen of the C=N bond and that there was no interaction with the

phenol groups in the ligand. Although this gave us an insight into the bonding of the compound it did not provide sufficient evidence to the exact structure of the complex.

Table 3.1 A comparison of some of the major absorption bands in the FT-IR of the methylbenzoxazole **2.10** and the complex **2.10a**. Values in cm^{-1}.

Absorption area	**Ligand 2.10**	**Complex 2.10a**
3300-3000	3082 (w) Broad band	3243 (m) Sharp band
1650-1550	1627 (w)	1631 (m)
	1608 (w)	1591 (m)
	1572 (w)	

Earlier a range of solvents were tested to look at the solubility of the complex **2.10a**. After a few days it was observed that very small crystals had grown from some of the solutions, but with a great deal of decomposition associated with it.

However a crystal of X-ray diffraction quality could be recovered from a *N,N*-dimethylformamide solution of the compound. Figure 3.3 shows a perspective view of the crystal structure of **2.10a**, together with the labelling scheme used in the structural analysis. This crystal structure was the first structural evidence of the bonding of the 4-hydroxybenzoxazole ligands and compares well to crystal data that was recently recorded by Jones *et al*.,[12] for the un-functionalised benzoxazole and 2-methylbenzoxazole complexes with $PdCl_2$, as well as the data collected by Ito *et al*.[25] on the 2-(benzoxazol-2-yl) phenol complex with $PdCl_2$.

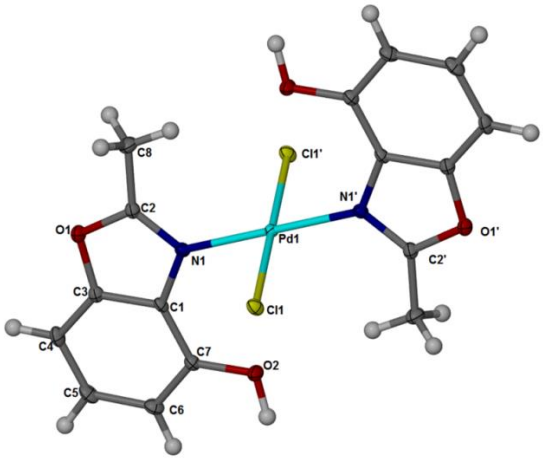


Figure 3.3 Molecular structure of benzoxazole complex **2.10a** with the labeling scheme. Unlabelled atoms are related to the labelled atoms by a centre of inversion (the labels for the most important atoms of the centro-symmetric part are shown, marked with '). All non-hydrogen atoms are drawn as displacement ellipsoids at 50 % probability and H atoms are shown as spheres of arbitrary radius. Solvent of recrystallization (DMF) was removed for clarity.

2.10a crystallised out in the triclinic space group *P−1.* The asymmetric unit consisted of half a molecule which is situated on an inversion centre, as well as one molecule of *N,N*-dimethylformamide. The Pd(II) ion was coordinated in a *trans* square-planar configuration to the nitrogen atoms of the C=N bond of two ligands of **2.10** (κ^1*N)* as well as two chloride atoms. No visible interactions between the Pd(II) ion with the phenol groups were observed. This data validated the findings from the FT-IR spectroscopy analysis.

The palladium centre displayed a square planar geometry, with the angles of N1-Pd1-Cl1 and N1-Pd1-Cl1' close to right angles [90.45(3)° and 89.55(3)° respectively] and the linear angles for Cl1-Pd1-Cl1' and N1-Pd1-N1' [180.00° and 180.00° respectively, see Table 3.2 for more bond angles and lengths] giving further evidence to that. The bond lengths for Pd1-Cl1 was found to be 2.3038(4) Å and for Pd1-N1 2.0130(12) Å and compared well to values found in literature.[12, 25]

Interestingly it was also observed that the bond length of the bond C2-N1 was only slightly longer in the complex than in the ligand **2.10** [1.3036(18) Å versus 1.3006(19) Å, thus explaining the small shifts in the FT-IR spectrum.

Table 3.2 Selected bond lengths (Å), angles and torsion angles (°) for complex **2.10a**. Numbering can be seen in Figure 3.3.

Pd1-Cl1	2.3038(4)	C2-N1	1.3036(18)
Pd1-N1	2.0130(12)	C2-O1	1.3521(17)
N1-Pd-N1’	180.00	N1-Pd1-Cl1	90.45(3)
Cl1-Pd1-Cl1’	180.00	N1-Pd1-Cl1’	89.55(3)
C1-N1-C2	106.29(12)	C1-N1-Pd1	129.03(10)
Cl1-Pd1-N1-C2	108.90(1)		

It was further shown that the complex was also involved in intermolecular hydrogen bonds (O-H···O, see Table 3.3 and Figure 3.4) with two molecules of *N,N*-dimethylformamide to form a discrete chain. These and other close contact interactions stabilise the moieties to form a network of integrated molecular structures.

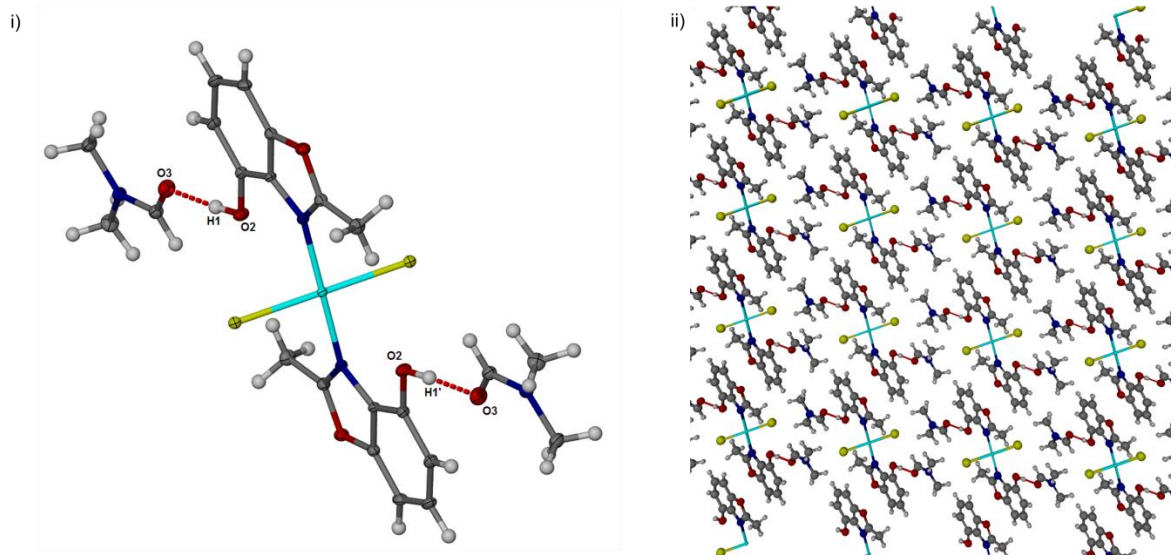


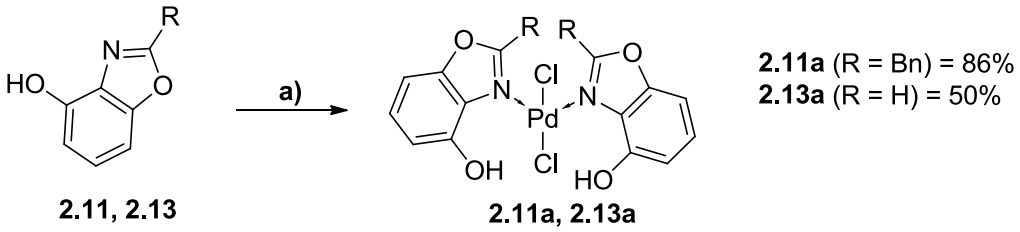
Figure 3.4 Hydrogen bonding in the structure of benzoxazole **2.10a**: i) Showing the individual molecules viewed down the *a* axis, as displacement ellipsoids drawn at 50 % probability; ii) Molecular packing viewed along the *a* axis. Molecules are shown in the ball-and-stick representation. Hydrogen bonds are represented as red dashed lines.

Table 3.3 Hydrogen bond geometry for benzoxazole **2.10a** (Å, °)

D-H···*A*	**D-H**	**H···*A***	**D···*A***	**<(DH*A*)**
O2-H1···O3^{i}	0.883(16)	1.750(16)	2.6294(15)	174(2)

Symmetry codes: (i) 1+x, y, z

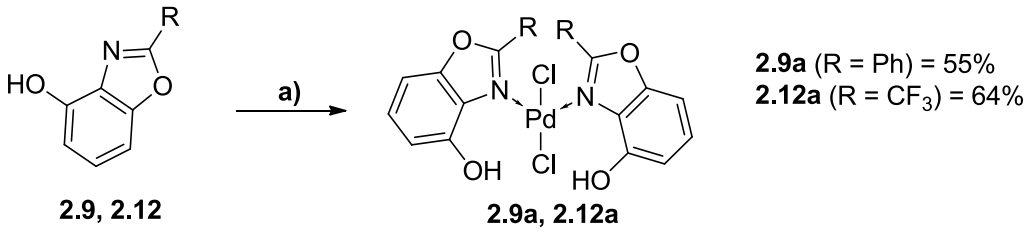
With this data in hand our attention was turned to the synthesis of the $PdCl_2$ complexes of ligands **2.9** (R=Ph) and **2.11-2.13** with $[PdCl_2(MeCN)_2]$ as precursor. Due to the low solubility of ligands **2.11** (R=Bn) and **2.13** (R=H) in dichloromethane another solvent had to be found to perform the reactions in. These ligands were soluble in mostly polar solvents (most of the alcohols, tetrahydrofuran, *N,N*-dimethylformamide, dimethylsulfoxide etc.), but earlier work proved that these solvents were not a good choice, mainly due to the degradation of the coordination compounds when heated in these solvents. Of the choices available tetrahydrofuran seemed the most suitable and for the application, but the palladium precursor was only soluble in dichloromethane. A mixture of tetrahydrofuran and dichloromethane (5:2, v/v) was found to give the best solubility for both ligand and metal, and subsequent reactions were performed in these mixtures at room temperature (Scheme 3.4). Ligand **2.11** (R=Bn) formed an almost instantaneous precipitation and was left to stir for four hours to yield **2.11a** in 86%, whereas **2.13** (R=H)needed to stir overnight to form **2.13a** in 50% yield. Efforts to recover the rest of the product by crystallisation of the filtrate ended in decomposition.



Scheme 3.4 Synthesis of complexes **2.11a** and **2.13a**. *Reagents and reaction conditions*: a) $[PdCl_2(MeCN)_2]$ (0.5 equiv.), THF/DCM (5:2, v/v), rt

Ligands **2.9** (R=Ph) and **2.12** (R=CF_3) did not have the same solubility problems and the reactions were performed in dichloromethane (Scheme 3.5). It was found that the precipitation of the product progressed slower than for methylbenzoxazole **2.10.** In the case of ligand **2.9** (R=Ph) the coordinated product **2.9a** was partially soluble in dichloromethane and only a small amount of product was collected by filtration. The rest of the material was dissolved in a large amount of warm dichloromethane and allowed to slowly crystallise out in a fridge at −20 °C. After a few days small light-orange crystals formed which were collected

by filtration to return a combined yield of 55%. The synthesis of **2.12a** proceeded without any complications, returning a yield of 64%.



Scheme 3.5 Synthesis of complexes **2.9a** and **2.12a**. *Reagents and reaction conditions*: a) $[PdCl_2(MeCN)_2]$ (0.5 equiv.), DCM, rt

These compounds also revealed the same solubility characteristics that **2.10a** had and it appeared that solubility of the complexes increased as the R-group on the 2-position of the benzoxazole ligand increased in size. All the compounds were only stable in solution for short periods before decomposing started (few days at most, with Pd(0) leaching out of the solution), which heavily retarded their characterisation and ability to form X-ray diffraction quality crystals. In most of the cases very small crystals formed, but they usually did not last long before decomposition of the product occurred while still in contact with the solvent. This phenomenon was also noted by Jones *et al.*[12] The compounds were all isolated as light- to yellow powders and were stable at room temperature when stored in vials kept on the bench-top; however it appeared as if it was not the case for **2.12a**. The colour of the complex slowly darkened over time, possibly due to the formed complex slowly decomposing.

FT-IR spectroscopy of the coordination compounds all revealed comparable features with that of complex **2.10a** (see Figure 3.5 for an example of the FT-IR spectra of ligand **2.9** (R=Ph) and the complex **2.9a**, as well as Table 3.1 and Table 3.4 for comparison).

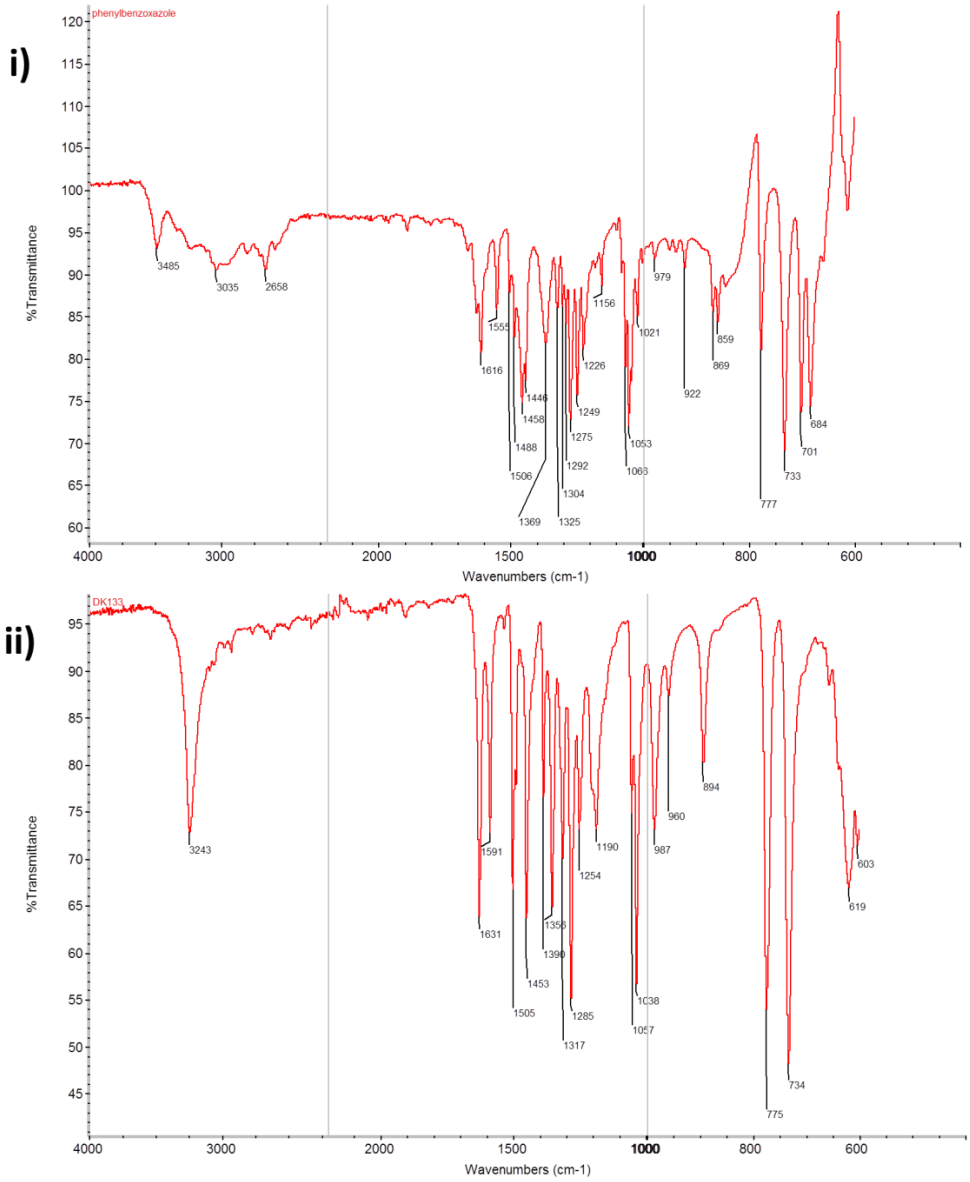


Figure 3.5 FT-IR spectra of i) phenylbenzoxazole **2.9** and ii) the Pd complex **2.9a.**

All the coordination complexes revealed the appearance of a sharp absorption peak that correlates to a phenol O-H stretch (3490-3105 cm^{-1}), probably due to the disruption of the hydrogen bonding to the nitrogen of the benzoxazole, as well as sharper and more defined features in the rest of the aromatic C-H absorption frequencies. In all of the cases there were appreciable shifts in the area between 1650-1550 cm^{-1}, correlating to the C=N and C=C absorption frequencies. These shifts indicated that the coordination of the complexes also occurred through the nitrogen atom of the C=N bond.

Table 3.4 A comparison of some of the major absorption bands in the FT-IR of the benzoxazoles **2.9, 2.11-2.13** and their complexes **2.9a, 2.11a-2.13a**. Values in cm^{-1}.

Absorption area	Ligand 2.9	Complex 2.9a	Ligand 2.11	Complex 2.11a
3500-2600	3485 (w)	3293 (m) Sharp band	3108 (w) Broad band	3114 (w) Broad band
	3035 (w)	3056 (w)		2988 (w)
	2658 (w)			2882 (w)
1650-1550	1631 (w)	1635 (m)	1632 (w)	1630 (w)
	1616 (m)	1606 (m)	1609 (m)	1577 (w)
	1555 (w)	1550 (m)	1569 (m)	

Absorption area	Ligand 2.12	Complex 2.12a	Ligand 2.13	Complex 2.13a
3500-2600	3277 (w) Broad band	3447 (w)	3114 (m) Broad band	3284 (m) Sharp band
	3053 (w)	3278 (w)		3103 (m) Sharp band
				3053 (w)
1650-1550	1622 (m)	1635 (m)	1628 (w)	1630 (m)
	1584 (m)	1609 (w)	1605 (m)	1620 (m)
		1582 (m)		

As in the case of **2.10a** the only data recovered from mass spectrometry was that of a large peak that is associated with the starting ligands. NMR spectroscopy of the complexes also revealed the same characteristics as that of complex **2.10a**. Due the general insolubility of the compounds, the exceptions being **2.9a** and **2.12a**, all the NMR spectroscopy work were

performed in deuterated dimethylsulfoxide as saturated heterogeneous solutions.. Due to the low concentration of the analyte solutions ^{13}C NMR spectroscopy yielded no usable information. Complex **2.13a** however did not fully dissolve and had to be heated to go into solution. When ^{1}H NMR spectroscopy was performed on the solutions of the complexes some general characteristics were observed. In all the cases, except for **2.12a** and to an extent **2.13a**, a mixture of what looked like starting ligand and product could be seen. In the case of **2.12a** and **2.13a** only the signals that correlated with the starting ligand could be observed. The solutions, except **2.12a**, were also analysed at 50 °C to observe if the two products were due to some rotational isomers that were formed in the solutions. In all the cases it was observed that the signals corresponding to the complex disappeared and mostly the signals of the starting ligand remained visible. When the compound was again run at room temperature only the starting ligand signals were visible. For complex **2.9a**-**2.11a** some product was still visible, but only in very low concentrations.

In an article from Haneda *et al*.,[26] on the ligand effects of 2-(2-pyridyl)benzazole-Pd complexes, it was also noted that ligand dissociation was occurring in varying degrees in their complexes when analysed by ^{1}H NMR spectroscopy as solutions in deuterated dimethylsulfoxide. Their argument regarding the dissociation was mainly based on the N-Pd bond strength that varied according to the electronic effects of the individual azoles, with the benzimidazole derivative showing the least dissociation followed by the benzoxazole and the benzothiazole derivatives. Casu *et al*.[27] observed in their ^{1}H NMR spectroscopy study of Pt(II) benzoxazole ligands that, over a period of 70 minutes, the resonances of free ligand increased in the solution. Their work pointed to a displacement reaction of the ligand with the softer dimethylsulfoxide donor aided by a possible interaction of the halide coordinated to the Pt(II) centre. In our case it appeared as if the ligand dissociation could be a combination of these two effects and that the Pd-N bond of the complex not being very strong, due to the nitrogen being a harder donor and the softer Pd would rather form bonds with the dimethylsulfoxide. The influence of the solvent became quite apparent in the way that the spectra changed as the complexes went into solution, with the signals for the free ligand becoming more dominant and the complex signals disappearing. No visible shifts occurred for the deuterated dimethylsulfoxide signal to support the idea of the displacement, but the concentration of the solutions are usually very low and it could be possible to miss a small shift in the large solvent signal.

The effect of the ligand dissociation was best displayed when a ^{1}H NMR spectrum of **2.9a**, in deuterated chloroform to which a few drops of deuterated dimethylsulfoxide was added to increase the solubility (Figure 3.6), was collected at room temperature and at 50 °C.

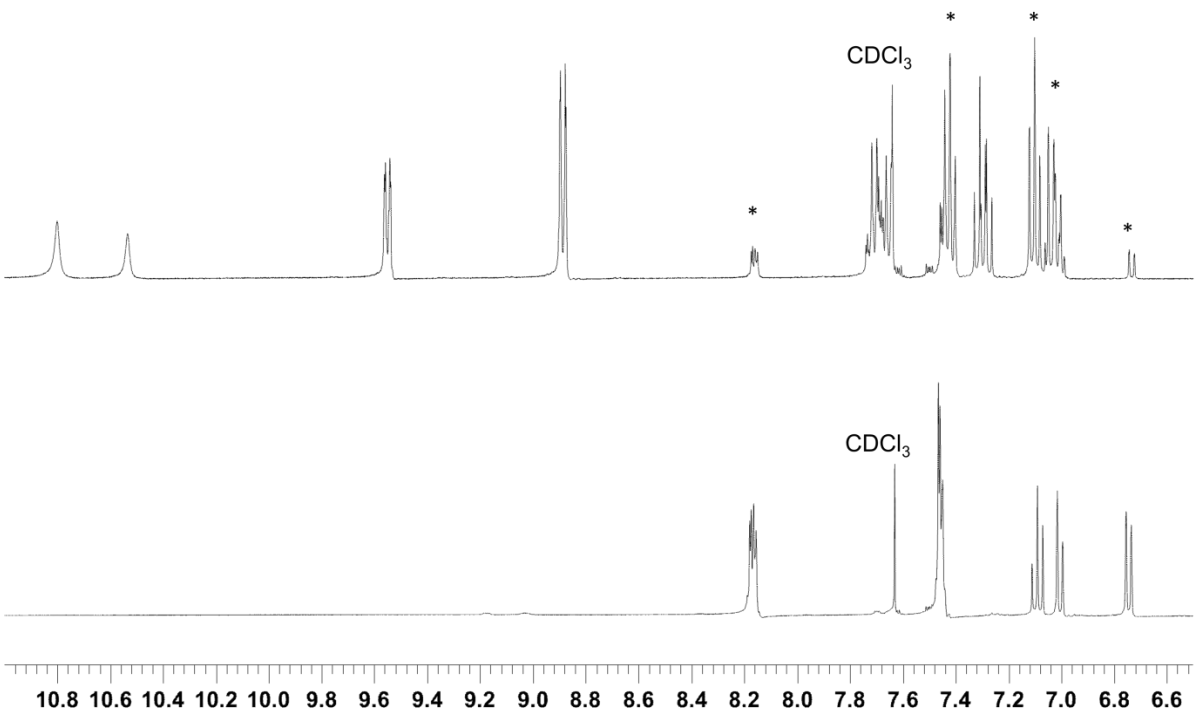


Figure 3.6 An expansion (6.50-11.0 ppm) of the ^{1}H NMR spectra of the palladium complex of **2.9a** at room temperature (top) and at 50 °C (bottom) in $CDCl_3$ and a few drops of DMSO-d_6. * indicates the signals that corresponds with ligand **2.9** (R=Ph).

At room temperature the signals corresponding to the ligand **2.9** (R=Ph) were seen as the minor product, marked with an asterisk (*) (Figure 3.6, top spectra). When the spectra was taken at 50 °C (Figure 3.6, bottom spectra) the signals corresponding to the complex **2.9a** completely disappeared and only the signals for the free ligand **2.9** was left.

Some of the crystals collected from the recrystallization of complex **2.9a** from dichloromethane were deemed as good enough for X-ray diffraction. Figure 3.7 shows a perspective view of the crystal structure of **2.9a**, together with the labelling scheme used in the structural analysis.

2.9a crystallised out in the monoclinic space group *Pc.* The asymmetric unit consisted of two molecules of the complex (marked as A and B) as well as two molecules of dichloromethane that are related with a glide plane perpendicular to [0, 1, 0] and a glide component of [0, 0,

½]. In both of the structures the Pd(II) ion was coordinated in a *trans* square-planar configuration to the nitrogen atoms of the two ligands of **2.9** (R=Ph) (κ^1*N)* as well as to two chloride atoms.

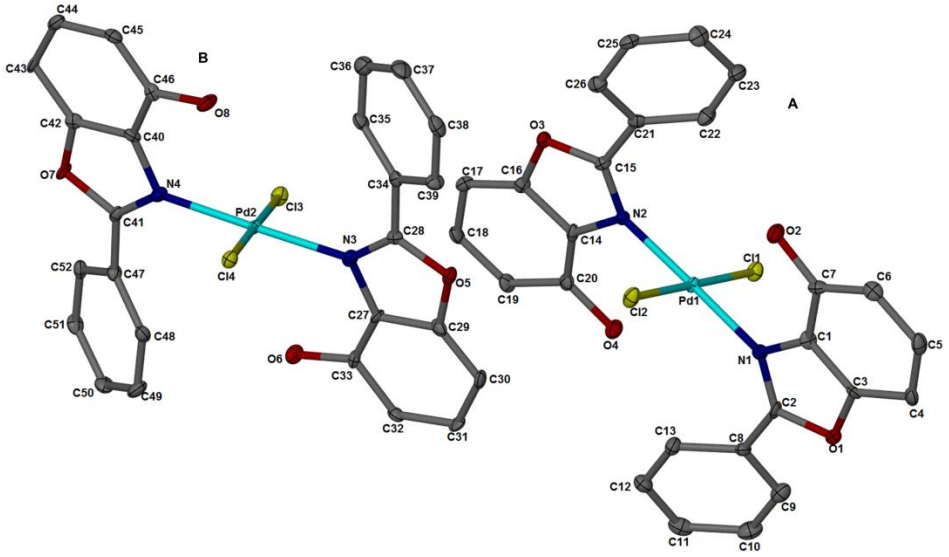


Figure 3.7 Molecular structure of benzoxazole complex **2.9a** with the labeling scheme. All atoms are drawn as displacement ellipsoids at 50 % probability and H atoms and the solvent molecules of recrystallization (DCM) were removed for clarity.

During the solving of the crystal structure the possibility of a pseudo merohedral twinned structure appeared. Twinned structure refinement using BASF and TWIN parameters was followed and a Flack x parameter of 0.44(3) was returned, revealing that this was the absolute structure and very little overlap occurred.[28] Intramolecular hydrogen bonds (O-H···Cl, see Table 3.5) also stabilised the molecular structures of the complexes. The benzene ring on the 2-position was twisted with respect to the heterocyclic rings and the dihedral angle between the least-squares planes of the benzene molecule [C8-C13] and the corresponding benzoxazole ring was found to be 27.39(15)°.

Table 3.5 Intramolecular hydrogen bond geometry for benzoxazole **2.9a** (Å, °)

D-H···*A*	**D-H**	**H···*A***	**D···*A***	**<(DH*A*)**
O4-H3···Cl1	0.92(2)	2.28(3)	3.186(40	171(5)
O2-H2···Cl2	0.93(2)	2.32(3)	3.232(4)	169(5)
O6-H1···Cl3	0.93(2)	2.32(4)	3.177(4)(3)	155(7)
O8-H4···Cl4	0.92(2)	2.28(4)	3.151(4)	156(6)

Analysis of the other ring systems, using the same principle as above, returned values of 24.97(94)° [C21-C26], 25.48(18)° [34-39], 26.78(16)° [C47-C52] respectively. The angles of N-Pd-Cl around the square planar palladium centres displayed values close to right angles [88.85(16)-91.70(16)° for Pd1 and 89.21(13)- 91.35(16)° for Pd2] and approximately linear angles for Cl-Pd-Cl and N-Pd-N [179.01(8)° and 178.9(2)° for Pd1, 179.27(7)° and 179.0(2)° for Pd2 respectively, see Table 3.6 for more bond angles and lengths] giving further evidence to that. The bond lengths for Pd-Cl were found to be 2.29065(16)- 2.3003(16)Å and for Pd-N 2.019(5)- 2.038(5)Å and compared well to the values found for complex **2.10a** as well as in the literature.[12, 25]

Table 3.6 Selected bond lengths (Å) and angles (°) for complex **2.9a**. Numbering can be seen in Figure 3.7.

Pd1-Cl1	2.3003(16)	Pd2-Cl3	2.29065(16)
Pd1-Cl2	2.2882(17)	Pd2-Cl4	2.2990(17)
Pd1-N1	2.019(5)	Pd2-N3	2.032(5)
Pd1-N2	2.038(5)	Pd2-N4	2.034(5)
N1-C2	1.312(8)	N3-C28	1.310(8)
N2-C15	1.305(8)	N4-C41	1.307(8)
N1-Pd1-N2	178.9(2)	N3-Pd2-N4	179.0(2)
N1-Pd1-Cl2	90.24(16)	N3-Pd2-Cl3	90.21(16)
N2-Pd1-Cl2	88.85(16)	N4-Pd2-Cl3	89.21(13)
N1-Pd1-Cl1	89.22(16)	N3-Pd2-Cl4	89.25(16)
N2-Pd1-Cl1	91.70(16)	N4-Pd2-Cl4	91.35(16)
Cl2-Pd1-Cl1	179.01(8)	Cl3-Pd2-Cl4	179.27(7)

The molecular packing of the structures was largely dominated by π···π interactions between the six-membered aromatic rings of the benzoxazole moieties (see Figure 3.7 for numbering and Figure 3.8 for the packing diagrams). The 6-membered ring (C14-C20) of A were connected linearly along the *c* axis to two molecules of B (C27-C33) via offset π···π interactions. Due to the connections being generated by two different symmetry operators

two values were recorded for the contact distances [centroid of 6-membered ring (C27-C33)··· centroid of 6-membered ring (C14-C20) = 3.629(3) Å for (X, Y, Z) and centroid of 6-membered ring (C27-C33)··· centroid of 6-membered ring (C14-C20) = 3.521(3) Å for (X, Y, 1+Z)]. The individual molecules of A and B were also connected to an equivalent molecule (A to A and B to B) via π···π interactions of the 6-membered rings perpendicular to the *c* axis [centroid of 6-membered ring (C1-C7)··· centroid of 6-membered ring (C1-C7) = 3.565(3) Å and centroid of 6-membered ring (C40-C46)··· centroid of 6-membered ring (C40-C46) = 3.575(3) Å]. This integrated system of interactions formed a tight crystal packing structure that has overlapping molecules in a 2D network, the first along the *c* axis and then also as step-like connections along the *b* axis. These interactions are also further stabilised by other close contact interactions, especially those of the dichloromethane molecules with the various parts of the molecules A and B.

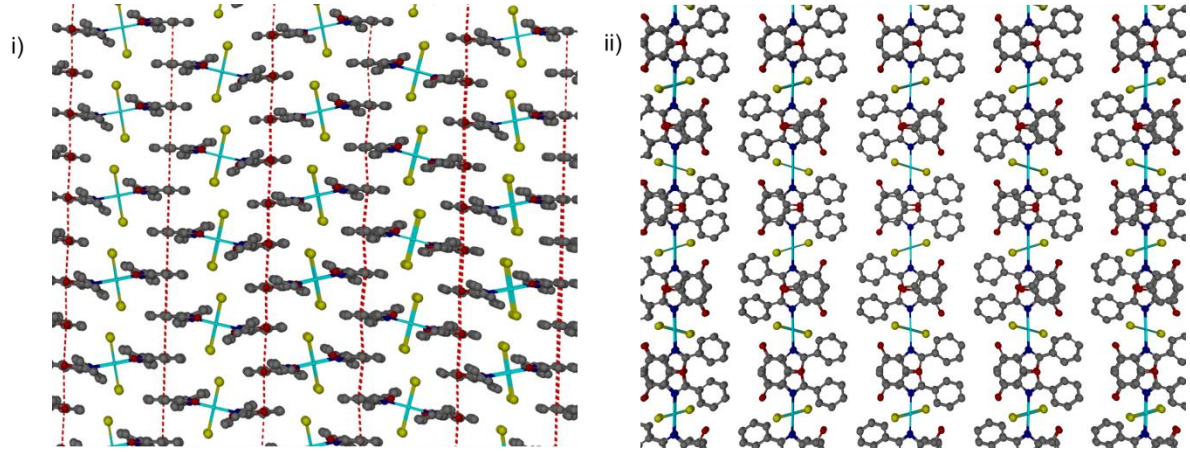


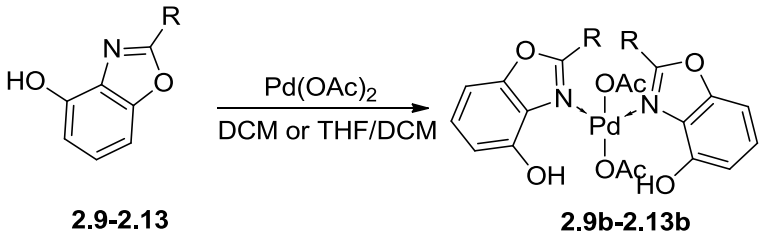
Figure 3.8 Molecular packing arrangement of **2.9a** to showcase the 2D network formed by π···π interactions: i) Showing the π···π interactions between the centroids of the aromatic rings as red dotted lines; ii) Molecular packing viewed along the *c* axis. Molecules are shown in the ball-and-stick representation. Hydrogen atoms and recrystallization solvent removed for clarity.

With these complexes in hand the attention was turned to the synthesis of the $Pd(OAc)_2$ derivatives of the ligands.

3.2.3 $Pd(OAc)_2$ precursors

The syntheses of the [$Pd(OAc)_2$] precursors were performed in the same manner as for the $PdCl_2$ versions. Ligands **2.9**-**2.13** were dissolved in either dichloromethane (**2.9**, **2.10**, and **2.12**) or tetrahydrofuran (**2.11** and **2.13**) at room temperature (Scheme 3.6). To this solution

of the ligand was added $Pd(OAc)_2$ (L:M = 2:1) as a solid or as a solution in dichloromethane and the reaction was stirred at room temperature overnight.



2.9-2.13 **2.9b-2.13b**

Scheme 3.6 Proposed synthesis of the $Pd(OAc)_2$ precursors from ligands **2.9-2.13**.

The reaction of **2.9** (R=Ph) and $Pd(OAc)_2$ in dry dichloromethane yielded an orange-red solution, with minimal precipitation. Thin layer chromatographic analysis of the reaction revealed that the ligand was consumed and a new, very polar, compound had formed after stirring for 24 hours at room temperature. The solid was filtered, but was found to dissolve in the subsequent wash with dichloromethane. The solvent was removed to yield an orange-red solid, but attempts to get it back into dichloromethane was not successful and heating for a prolonged period revealed the formation of a dark coloured solid and the reaction was abandoned. The previous synthesis of **2.9a** has shown that the product was slightly soluble in dichloromethane and that performing the reaction at higher concentrations helped with formation of a precipitate. It was reasoned that this was also the case for **2.9b** and the reaction was therefore repeated at a higher concentration (0.093 M *vs* 0.056 M). Within a period of two hours some precipitation had occurred and it was decided to remove the precipitate after two and a half hours. The product was filtered and washed with cold dichloromethane and hexane, but only a small amount of product was recovered and the solvent of the filtrate was removed to yield a yellow solid. Thin layer chromatography of the filtrate revealed a very faint spot, indicative of ligand **2.9**, and a more polar compound that had the same appearance as the previous reaction. Intriguingly the colour of the reaction and the precipitate was yellow, which was quite different from the previous reaction. It was decided to re-dissolve the filtrate fraction in dichloromethane and place in a fridge at −20 °C to see if the product could be isolated in this manner. The product did not dissolve easily in a concentrated solution of dichloromethane, thus more dichloromethane was added and the solution only slightly warmed. After about two weeks small yellow crystals were collected.

The reactions of benzoxazoles **2.10** (R=CH_3), **2.11** (R=Bn) and **2.13** (R=H) with $Pd(OAc)_2$ proceeded without difficulty. Products **2.10b** and **2.13b** formed almost instantaneous precipitations that could be collected by filtration, while **2.11b** had to be precipitated with

hexane from a concentrated solution of dichloromethane. The reaction of ligand **2.12** ($R=CF_3$) with $Pd(OAc)_2$ proceeded very slowly and efforts to recover the product from the reaction solution ended with the precipitation of Pd(0) from the solution. If the reaction was left for a longer period decomposition occurred and it was decided not to pursue the synthesis of this precursor due to the instability of the products that was formed.

The solubility of the products **2.9b-2.13b** were in most cases better than for the $PdCl_2$ precursors while in the reaction media. As soon as the solvent was removed the product did not go back into solution very easily and in most cases heating was needed to fully dissolve the product. **2.13b** however was virtually insoluble in all the organic solvents with **2.10b** also being problematic. As in the previous case the solubility of the compounds increased as the R-group on the 2-position of the benzoxazole increased, with most products being soluble to some extent in polar solvents (dimethylsulfoxide, *N,N*-dimethylformamide, acetonitrile, tetrahydrofuran) at low concentrations or at their reflux temperatures. **2.9b** and **2.11b** even exhibited average to good solubility in chlorinated solvents. The colour of the products was generally orange, but **2.9a** and **2.10b** were tan to light yellow, changing colour to orange when dissolved.

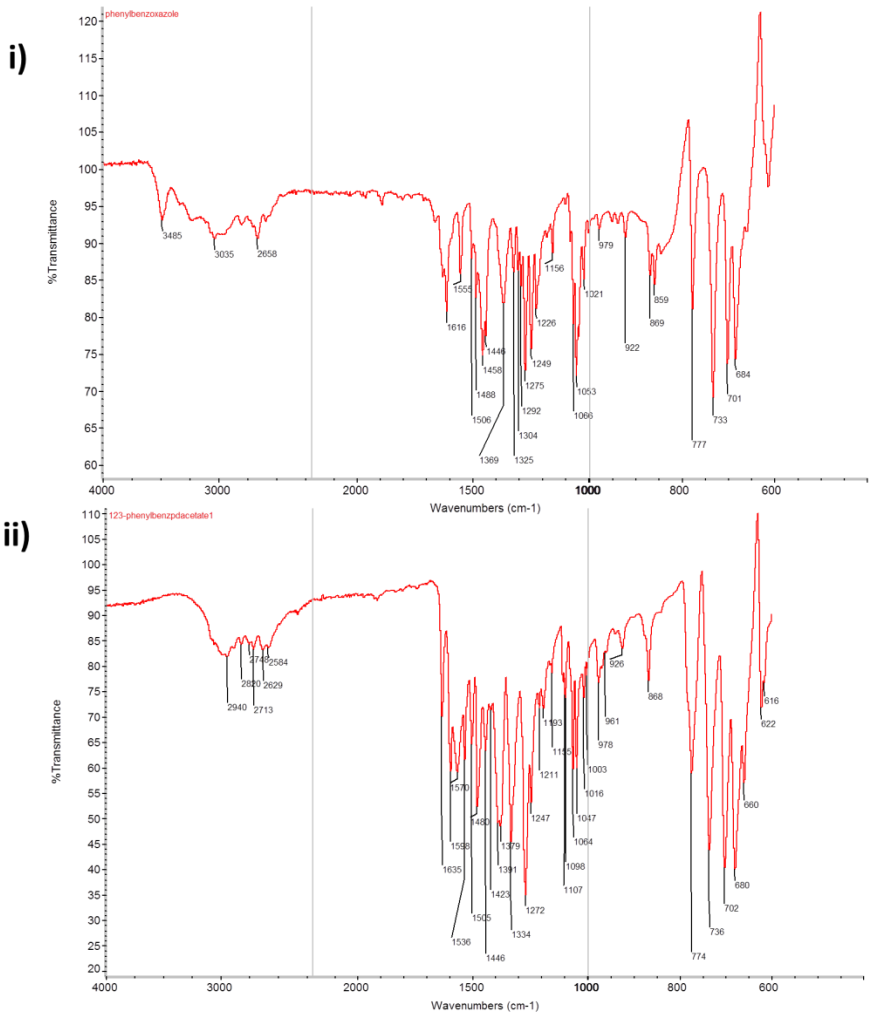


Figure 3.9 FT-IR spectra of i) phenylbenzoxazole **2.9** (R=Ph) and ii) the Pd complex **2.9b.**

The characterisation of the compounds again relied heavily on FT-IR spectroscopy (see Table 3.7, see also Table 3.1 and Table 3.4 for comparison). Analysis of the FT-IR spectrum of the precipitate of **2.9b** revealed some interesting changes from the ligand **2.9** (Figure 3.9). No corresponding absorption for the O-H vibration stretches could be found and a broad array of smaller absorptions could be observed in the area between 3050-2580 cm^{-1}, assigned to aromatic C-H stretching vibrations. The area around 1650-1550 cm^{-1} revealed shifts of the absorption bands to 1635, 1598 and a broad band at 1570 cm^{-1} According to the literature, the characterisation of the carboxylate groups coordinated to metal centres can be determined by the difference between the symmetric and asymmetric stretching vibrations of the CO_2^--groups.[29, 30] **2.9b** also revealed a strong absorption in the area around 1334 cm^{-1} that could be related to the symmetric stretching vibration of CO_2^-. The difference between the two strong bands at 1570 cm^{-1} (asymmetric vibration) and 1334 cm^{-1} equals 236 cm^{-1}, indicating a monodentate coordination of the acetate to the metal centre. This

data pointed to the formation of a complex very similar to **2.9a**, with acetates as counter ions, the only piece of data that could not be explained was the disappearance of the phenol stretching vibrations that was very explicit in the FT-IR spectrum of **2.9a**.

Table 3.7 A comparison of some of the major absorption bands in the FT-IR of the benzoxazoles complexes **2.9b-2.11b** and **2.13b**. Values in cm^{-1}.

Absorption area	Complex 2.9b	Complex 2.10b	Complex 2.11b	Complex 2.13b
3500-2600	2940 (w)	2935 (w)	3028 (w)	3057 (m) Sharp band
	3820 (w)	2824 (w)	2640 (w)	2982 (m)
	2629 (w)	2634 (w)		
1650-1550	1635 (w)	1632 (w)	1615 (w)	1615 (m)
	1598 (m)	1601 (m)	1602 (w)	1563 (m)
	1570 (m) Broad band	1561 (m) Broad band	1569 (m)	

^{1}H NMR spectroscopy of the solid, **2.9b**, in deuterated chloroform did not reveal any usable information due to the number of signals present, but when repeated in deuterated dimethylsulfoxide an assignable spectrum could be collected. The proton spectrum revealed the formation of a new compound with some shared characteristics with the ligand. Additionally another compound that could be an isomer of the product could be observed in the spectrum. The same sample was also recorded at 50 °C, with the most minor peaks disappearing, leaving only one set of signals. The signals comprised of two singlets at 1.77 and 1.91 ppm, accounting for the acetates in two different environments, a doublet of doublets at 6.78 ppm and three multiplets at 7.20, 7.61 and at 8.17 ppm. No clear signal for the -OH signal was visible, but some broad signals were found at about 10.50 ppm. From the NMR data no conclusive structure could be assigned to the molecule, but in most part it was in accord to what was seen in the FT-IR data.

For a matter of interest the reaction of **2.9** (R=Ph) with $Pd(OAc)_2$ was repeated at high dilution, using the same method as **2.11b**, and the product was precipitated with hexane out

of a concentrated solution of dichloromethane. The NMR spectrum of the red-orange product was the same as that of the precipitate of **2.9b** and used in the characterisation of the product.

The data was also confirmed by an X-ray diffraction structure elucidation of a crystal that was collected from the filtrate solution that was left to collect more of **2.9b** in the concentrated reaction. Figure 3.10 (i) shows a perspective view of the crystal structure of **2.9b**, together with the labelling scheme used in the structural analysis. Figure 3.10 (ii) shows the intramolecular hydrogen bonding of O2-H2···O4 in the asymmetric unit (see Table 3.8), further stabilising the molecular structure.

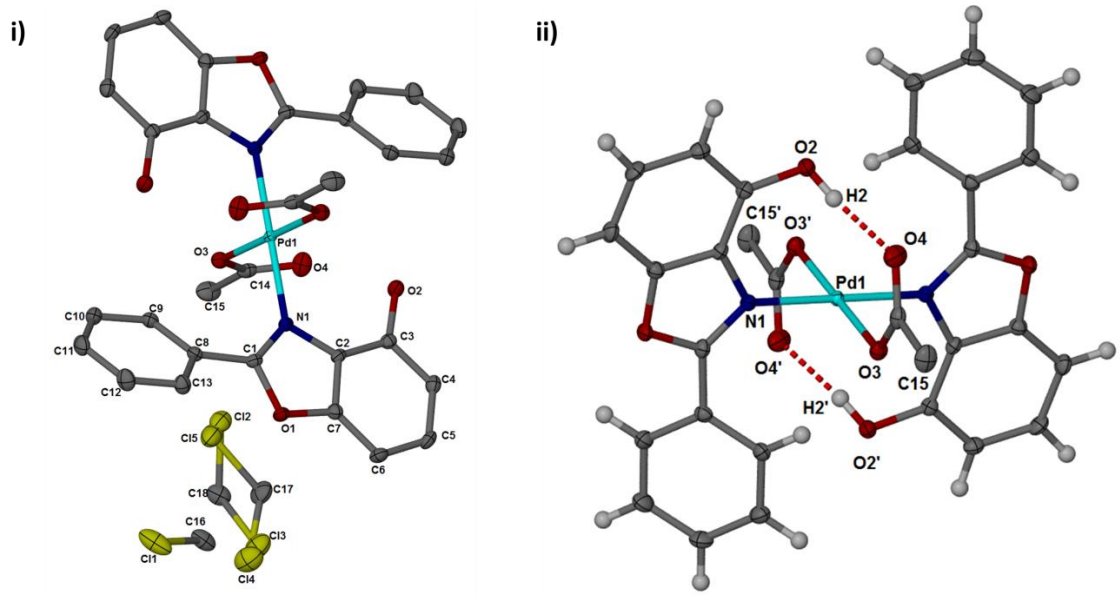


Figure 3.10 i) Molecular structure of benzoxazole complex **2.9b** with the labeling scheme, hydrogen atoms removed for clarity. Unlabelled atoms are related to the labelled atoms by a centre of inversion [the labels for the most important atoms of the centro-symmetric part are shown, marked with an apostrophe (‘) in (ii)]. ii) Intramolecular hydrogen bonding in the structure of **2.9b**. All non-hydrogen atoms are drawn as displacement ellipsoids at 50% probability and H atoms are shown as spheres of arbitrary radius. Solvent of recrystallization (DCM) and hydrogen atoms of C15 were removed for clarity.

Table 3.8 Intramolecular hydrogen bond geometry for benzoxazole **2.9b** (Å, °).

D-H···*A*	**D-H**	**H···*A***	**D···*A***	**<(DH*A*)**
O2-H2···O4	0.82(3)	1.81(3)	2.6232(18)	169(3)

2.9b crystallised out in the monoclinic space group *C2/c.* The asymmetric unit consisted of half a molecule which is situated on an inversion centre, as well as three molecules of dichloromethane after final refinement of the structure. Initially the one dichloromethane molecule was disordered over two positions and was later refined as two separate molecules of dichloromethane (Cl3-C18-Cl2 and Cl4-C17-Cl5), with an occupancy of 0.55 and 0.45 for the two carbon atoms. The Pd(II) ion was coordinated in a *trans* square-planar configuration to the nitrogen atoms of the two ligands of **2.9** (κ^1*N)* as well as to two oxygen atoms from the acetate moieties, in a linear fashion. No visible interactions between the Pd(II) ion with the phenol groups was observed. The X-ray structure of **2.9b** validated most of the data that was available.

The palladium centre displayed a square planar geometry, with the angles of O3-Pd1-N1 and O3'-Pd1-N1 close to right angles [89.61(5)and 90.39(5)° respectively] and the approximately linear angles for O3-Pd1-O3' and N1-Pd1-N1' [180.00° and 180.00(4)° respectively, see Table 3.9 for more bond angles and lengths] giving further evidence to that. The bond lengths for Pd1-O3 was found to be 2.0109(11) Å and for Pd1-N1 2.0324(13) Å.

Table 3.9 Selected bond lengths (Å), angles and torsion angles (°) for complex **2.9b**. Numbering can be seen in Figure 3.10.

Pd1-O3	2.0109(11)	C1-N1	1.311(2)
Pd1-N1	2.0324(13)	C2-O1	1.355(2)
N1-Pd-N1'	180.00(4)	O3-Pd1-N1	89.61(5)
O3-Pd1-O3'	180.00	O3'-Pd1-N1	90.39(5)

As in the case of **2.9a** the benzene ring on the 2-position was twisted with respect to the heterocyclic ring and the dihedral angle between the least-squares planes of the benzene molecule [C8-C13] and the corresponding benzoxazole ring was found to be 31.19(7)°, a slightly larger deviation than in the previous case.

The molecular packing of the structures was also largely dominated by weak, off-set π···π interactions between the six-membered aromatic rings of the benzoxazole moieties (see Figure 3.10 for numbering and Figure 3.11 for the packing diagrams) with the 5-membered

heterocyclic ring of a centro-symmetrical equivalent molecule [centroid of 6-membered ring (C2-C7)···centroid of 5-membered ring (O1-C7) = 3.7413(1) Å]. This arrangement of interactions forms 1D chains along the (110) line. Due to the array of symmetry operations another row of 1D chains are also formed at about a right angle to the other chains. The two 1D chains are interconnected and stabilised by close contact interactions between the molecules and especially the recrystallization solvent. The dichloromethane molecules trapped in the small voids in the crystal structure play a big role in the interconnection of the chain systems due to the various interactions it plays part in.

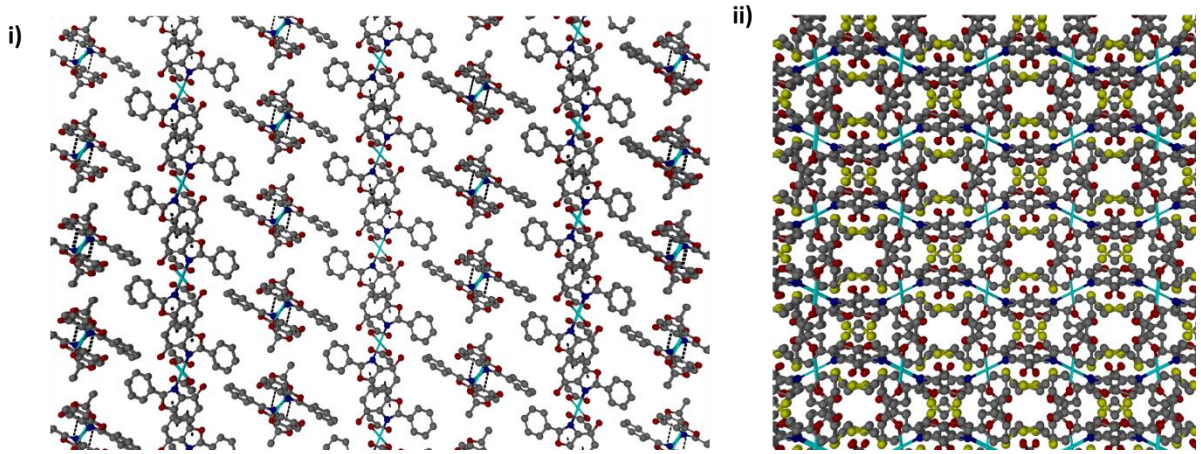


Figure 3.11 Molecular packing arrangement of **2.9b**: i) Showing the π···π interactions between the centroids of the aromatic rings as black dotted lines, viewed along (110). Solvent removed for clarity. ; ii) Viewed along the *c* axis to illustrate the patterns that form due to the positioning of the dichloromethane molecules in the crystal structure. Molecules are shown in the ball-and-stick representation. Hydrogen atoms removed for clarity.

The FT-IR spectroscopy data collected for the other complexes did not all follow the same trend as was seen for the phenylbenzoxazole complex **2.9b** (see Table 3.7 and Figure 3.9). All revealed a change in the adsorption vibration patterns in the areas between 3500-2600 cm^{-1} and 1650-1550 cm^{-1}, indicating the formation of a new compound that was coordinated to the metal through the nitrogen of the C=N bond. In all the cases there were also no stretches that corresponded with an O-H vibration, pointing to it possible taking part in the coordination to the Pd(II) centre. In the spectrum of **2.10b** (Figure 3.12), the same patterns of absorption were observed as seen in **2.9b**. This gave an indication that the formation of a complex with the Pd(II) and having the acetates intact has most probably occurred. **2.11b** and **2.13b** (Figure 3.12) however showed no absorption vibrations for the acetate groups on

the Pd(II) complex. This was perplexing, since the missing signals in the FT-IR spectra pointed to the possible formation of a metallocycle product.

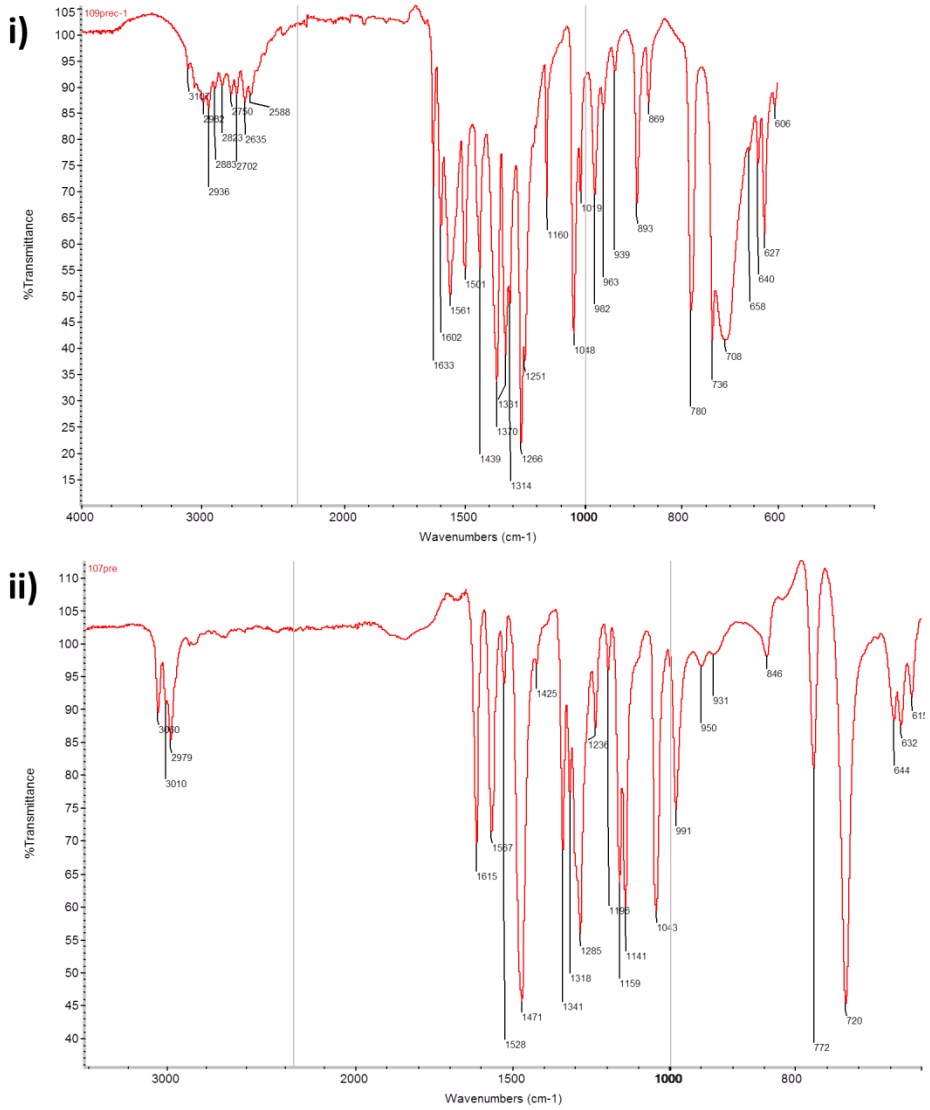


Figure 3.12 FT-IR spectra of complexes i) **2.10b** (R = Me) and ii) **2.13b** (R = H) to compare the stretching frequency patterns. See Table 3.7 for more information.

The ^{1}H NMR spectroscopic data of the compounds also gave support that coordination had occurred with the $Pd(OAc)_2$ owing to the newly formed signals in the aromatic area of the spectrum and the appearance of new signals relating to the 2-position of the benzoxazole. It however also appeared as if some partial dissociation of the ligand had occurred, but in general the resolution of the spectra was not very good due to the compounds' low solubility. **2.13b** was virtually insoluble in deuterated dimethylsulfoxide and this made it hard to make any valuable deductions from it, but with the data available it could be assessed that

coordination did occur, owing to the large downfield shift of the proton on the 2-position. **2.10b** and **2.11b** however shared some characteristics with **2.9b**. A singlet around 1.90 ppm that could be attributed to the -CH3 acetates coordinated to the Pd(II) centre as well as a very small, broad signal around 12 ppm, that could not be attributed to anything in any of the compounds and was judged to be some form of degradation in the compounds.

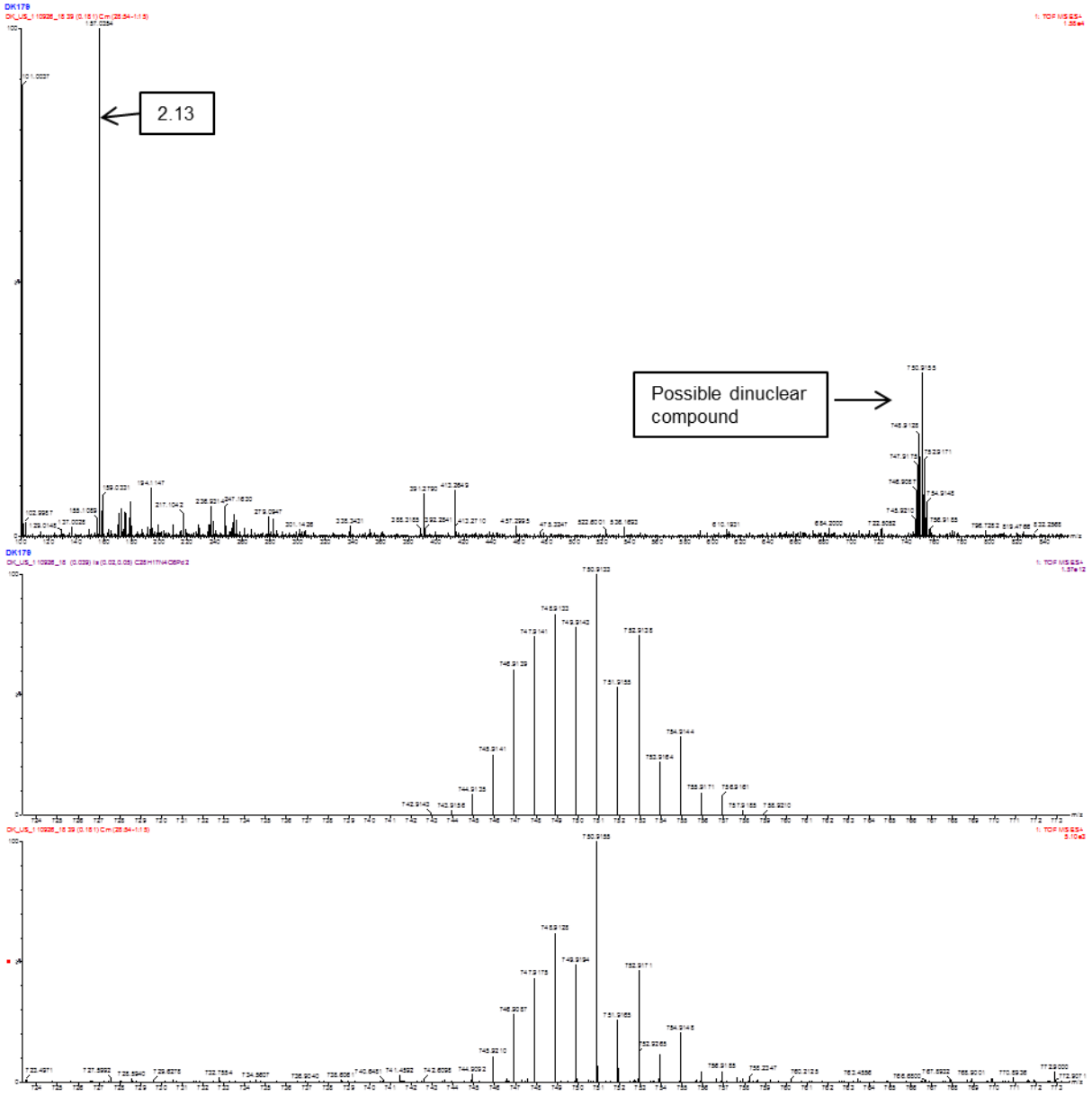


Figure 3.13 ESI+ mass spectrometryof **2.13b** (R = H) (top) with the indications for the peaks for the ligand and the possible dinuclear complex. Middle spectrum is a calculated one for the dinuclear compound and the bottom spectra the experimental spectrum.

Mass spectrometry of these compounds was frustrating in that no molecular ion peaks of [Pd**L**$_2$(OAc)$_2$]in either electron-spray positive or negative ionisation mode could be found. No peaks could also be found that correlated to the metallocycle compounds, however careful inspection of the spectra revealed clusters of peaks that had m/z values close to double that of the metallocycle compounds (see **2.13b** as example in Figure 3.13).

These clusters indicated the possible presence of different Pd isotopes and presented the possibility that the compounds were actually of a multi-nuclear nature. The m/z values recorded for the compounds can be viewed in Table 3.10. Isotope patterns of the experimental masses were evaluated against calculated patterns, generated from predicted masses of a compound of double the molar mass of that of the metallocycle product, and showed good correlation.

Table 3.10 M/z values of the clusters of peaks from the ESI+ mass spectroscopy of the complexes **2.9b-2.13b.**

Complex	m/z
2.9b	1055
2.10b	806
2.11b	1111
2.13b	751

From a concentrated solution of dichloromethane, kept at −20 °C, small crystals where collected of which only a few of X-ray diffraction quality could be isolated for **2.10b**. For **2.11b** a small crop of crystals could be isolated after a few days from a dichloromethane solution layered with diethyl ether.

These crystals were however very fragile and started to slowly disintegrate during the preparation of the diffraction sample. Careful handling of the crystals meant that structure data could be collected, but no satisfactory refinement was achieved due to disorder in the crystal structure caused by the slow evaporation of solvent from the samples during data collection. However what was quite unexpected were the molecular structures that were partially solved using this data (Figure 3.14).

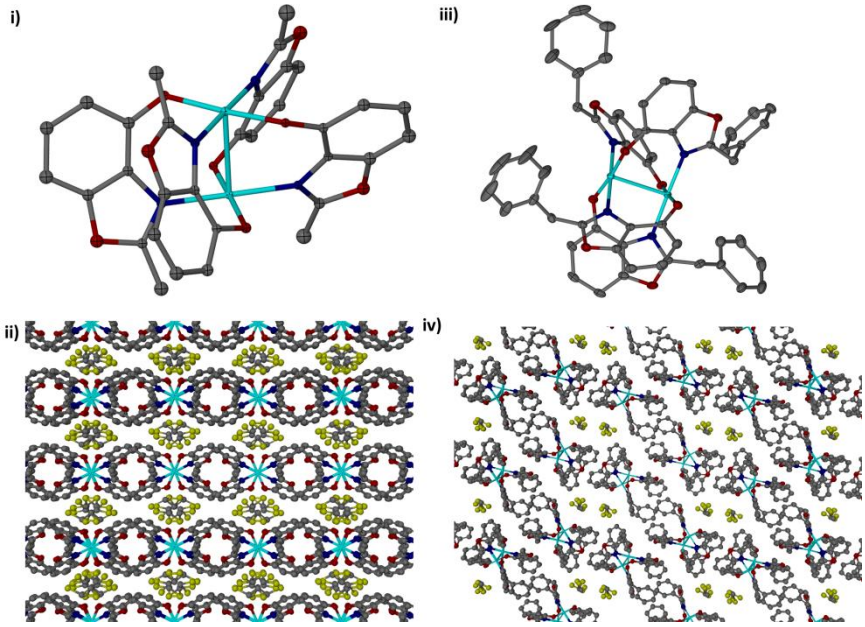


Figure 3.14 Molecular structure and packing diagrams of the complexes of **2.10b** and **2.11b**: i) Molecular structure of **2.10b**. ii) Packing diagram viewed down the *a* axis**.** iii) Molecular structure of **2.11b**. ii) Packing diagram viewed down the *a* axis. I) and iii) are drawn as thermal ellipsoids at 50% probability and ii) and iv) drawn as ball-and-stick representations. All hydrogen atoms are removed for clarity.

Both the molecular structures of **2.10b** and **2.11b** contained four ligand molecules bonded to two slightly distorted square planar Pd(II) atoms forming a paddlewheel like complex. Each ligand acted as an (N, O)-bidentate ligand with the nitrogen coordinating to one Pd(II) atom and the oxygen of the phenol group bound to the second Pd(II) atom. In this manner the nitrogen atoms and the oxygen atoms are situated *trans* to each other. This indicated that the acetate groups of the metal precursor indeed acted as a base as was the case in Li *et al.*,[7] deprotonating the phenol hydrogen and thus forming the complex. The bonding arrangement of the ligands caused the two Pd(II) atoms to sit close enough to each other to form Pd···Pd interactions and the ligands to form an up-down-up-down configuration. Both of the compounds formed integrated packing diagrams with the disordered dichloromethane molecules located in what appeared to be channels along the *a* axis. The packing in **2.11b** was not as close-fitting as in **2.10b**, due to the larger benzyl group on the 2-position.

The formation of similar binuclear coordination systems for the benzazole groups with Pd(II) atoms has been reported, of which examples of benzothiazole- and benzimidazole-derivatives being the most prominent.[31-38] In all of the cases the coordination occurs through the nitrogen of the C=N bond as well as another group (S or N) on the 2-position that forms

a bond with the Pd centres. The molecular structures of most of the molecules differ, but most of the compounds show *cis*, *cis* interactions. This is however the first example where this occurred with a coordinating group on the four position of the benzoxazole.

For the construction of more stable crystals it was decided to try and form them by slow evaporation of the solvents. This however led to precipitations, crystals that were too small or of low quality and ultimate decomposition of the complexes. Other solvents (*N,N*-dimethylformamide, tetrahydrofuran, benzene, chloroform) returned the same result. While acetonitrile also caused the decomposition of the complexes it was possible to obtain a crystal from **2.10b** that was good enough for X-ray diffraction. Figure 3.15 shows a perspective view of the crystal structure of **2.10b**, together with the labelling scheme used in the structural analysis.

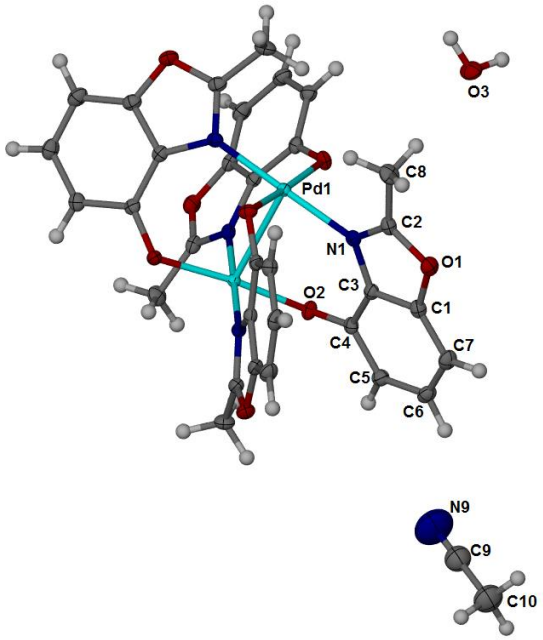


Figure 3.15 Molecular structure of benzoxazole complex **2.10b** with the labeling scheme. Unlabelled atoms are related to the labelled two 2-fold rotation axes. All non-hydrogen atoms are drawn as displacement ellipsoids at 50% probability and H atoms are shown as spheres of arbitrary radius.

2.10b crystallised out in the tetragonal space group *P4/ncc.* The asymmetric unit consisted of one molecule of ligand **2.10** which was bound through the phenol to one Pd(II) atom, as well as one molecule of water and acetonitrile. The hydrogen atoms of the acetonitrile were disordered over three positions in a linear fashion. As in the case of the disordered structures the complex also consisted of four ligands of **2.10** (related to each other *via* two 2-

fold rotation axes), acting as (N, O)-bidentate ligands with the nitrogen coordinating to one Pd(II) atom and the oxygen of the phenol group bound to the second Pd(II) atom, thus also forming the *trans* coordination pattern seen earlier. The Pd···Pd interaction was measured at 2.7774(4) Å, indicating a strong metal···metal interaction and comparing well with the values found in literature.[31-38]

The palladium centre displayed a slightly distorted square planar geometry, with the angles around Pd1 close to right angles [89.18(4)° - 90.78(4)°] and the approximately linear angles for O2-Pd1-O2' and N1-Pd1-N1' [173.70(4)° and 179.21(4)° respectively, see Table 3.11 for more bond angles and lengths] giving further evidence to that. The bond lengths for Pd1-O2 were found to be 1.9981(9) Å, Pd1-N1 2.0190(10) Å and C2-N1 1.2986(16) Å. The last two bonds are the shortest when compared to all of the other complexes and gave an indication that the bonds in this structure were somewhat stronger than for the other complexes. The nature of the bond of O2 with Pd1 [bond angle C4-O2-Pd1 = 122.45(8)°] caused the ligand not to coordinate to the Pd(II) centres in the same plane, forming a torsion angle for N1-Pd-Pd-O2 of −33.18(4)°. The opposite configuration was found in the *trans* ligand.

Table 3.11 Selected bond lengths (Å), angles and torsion angles (°) for complex **2.10b**. Numbering can be seen in Figure 3.15.

Pd1-O3	1.9981(9)	C2-N1	1.2986(16)
Pd1-N1	2.0190(10)	C4-O2	1.3300(16)
Pd···Pd	2.7774(4)		
N1-Pd-N1'	179.21(4)	O2-Pd1-N1	89.18(4)
O2-Pd1-O2'	173.70(4)	O2-Pd1-N1	90.78(4)
C4-O2-Pd	122.45(8)		

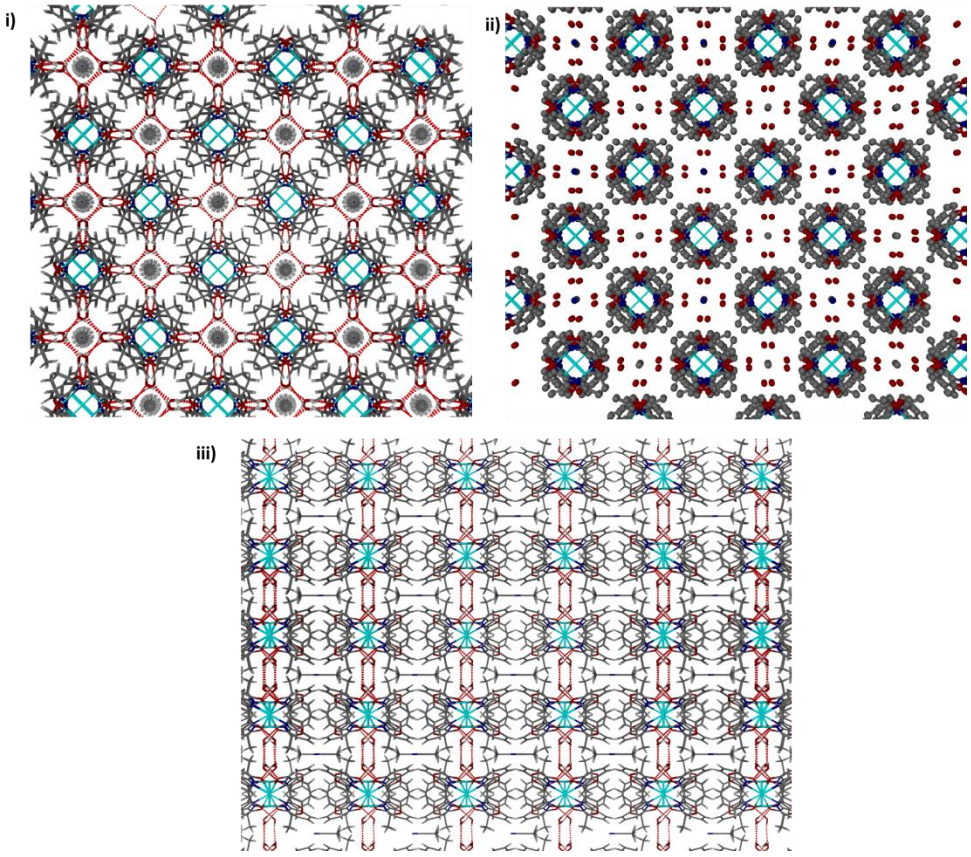
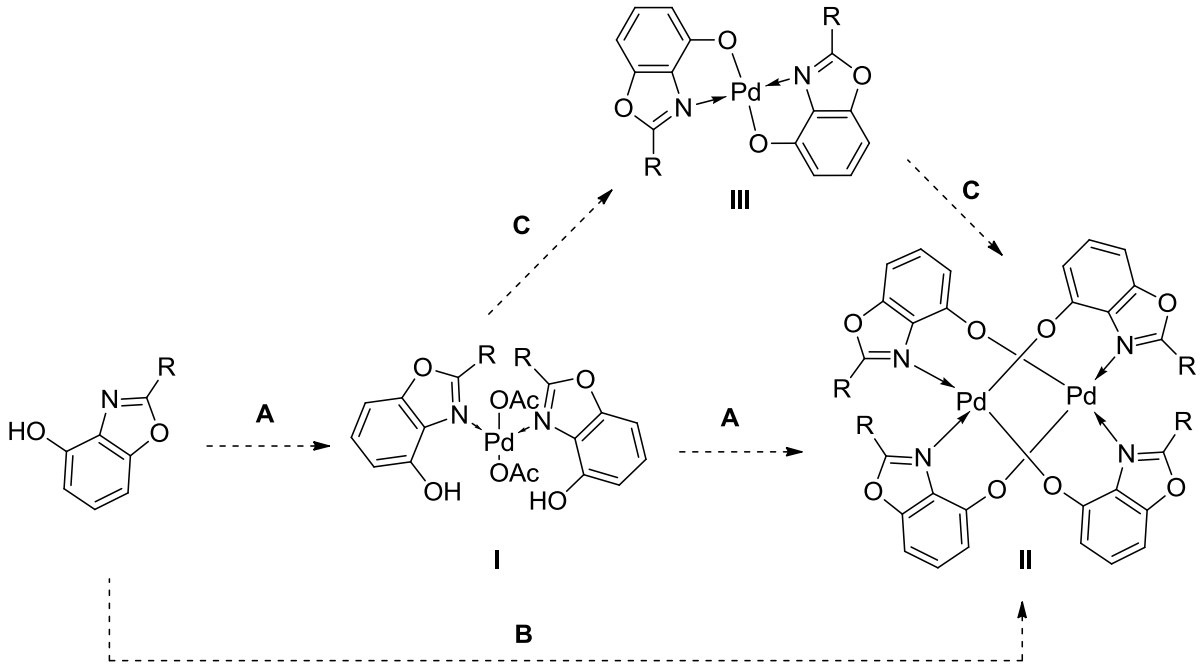


Figure 3.16 Molecular packing arrangement of **2.10b**: i) Showing the hydrogen bond framework, as red dotted lines, viewed down the *c* axis. ii) Hydrogen atoms removed to illustrate the directional packing of acetonitrile in voids. Molecules are shown in the ball-and-stick representation. iii) Showing the hydrogen bond framework, as red dotted lines, viewed down (-110). Molecules are shown in the stick representation in (i) and (iii).

The molecular packing of the crystal structure was dominated by the formation of an infinite 2D framework of hydrogen bonds (O-H···O) by the water molecules found in the voids between the molecules (Figure 3.16). Weak C-H···π interactions [C8···centroid of 6-membered ring (C1-C7) = 3.3281(16) Å] also helped with the stabilisation between the molecules. Furthermore the disordered acetonitrile molecules were packed head-to-tail, the direction alternating between adjacent cells, in well-defined solvent accessible voids in the crystal structure perpendicular to the *c* axis. This gave rise to a polar ordering of the solvent due to the dipole moments of the acetonitrile aligning in one direction.

3.2.3.1 Structure elucidation of complexes 2.9b-2.13b

Scheme 3.7 displays some of the possible reaction pathways that were envisaged for the formation of the complexes from the reaction between the benzoxazole ligands **2.9-2.13** and $Pd(OAc)_2$.



Scheme 3.7 Possible reaction pathways and products from the reaction of the benzoxazole ligands with $Pd(OAc)_2$.

Pathway A: This entailed the formation of an intermediate compound **I** as the mononuclear "kinetic product" (as seen for the crystal structure gathered for **2.9b**) due to the favourable coordination to the nitrogen atoms. With the reaction centres in close proximity the next step would entail the intramolecular formation of the bond between the phenol and the Pd centres. This process can occur very fast, but would probably be a slower process than the first one due to the reaction being dependent on the benzoxazole's ability to form the bond between the deprotonated phenol and the metal centre. The last reaction would be favoured due to the formation of acetic acid as conjugate acid, to produce the more favoured dinuclear product **II**.

Pathway B: This pathway involved the direct formation of compound **II** due to the action of the labile acetate counter ions of the Pd(II) salt as bases and this pathway would probably

correspond very much with pathway A, the only difference would be that any intermediate product would be very short lived and almost non-existing.

Pathway C: Another option was the formation of the five-membered metallocycle complex **III** from the initial reaction or from **I** and subsequent rearrangement to a more stable **II**. This route had however the most questions surrounding it. Lane *et al*.[4] reasoned that the 4-hydroxybenzoxazole's relatively low complex formation constants in their studies were due to a few factors. These included low ligand basicity, the higher electronegativity of the oxygen in the heterocycle, the orientation of the donating electrons which ties in with the last factor and the bonding distances between the nitrogen of the C=N bond and phenol. The combination of the factors can explain the absence of the five-membered metallocycle complexes in the literature since a molecule like complex **III** would form very strained bonds which would rather rearrange to the more stable **II**. An article by Shmakova *et al*.[39] (**1.38** in Scheme 1.5) illustrated this point very well, that the formation of the smaller ring size is not that favourable. A six-membered metallocycle-Cu complex was formed by the coordination of the nitrogen and the phenol on the 2-position of their benzoxazole, whereas there was no coordination interaction between the 4-hydroxy moiety and the nitrogen atoms, which would have formed the smaller rings. This was further evident in our work that no characterisation data was found to point to the formation of a compound like **III** and could thus be discounted as a viable pathway.

The inability of the phenol to stabilise coordination compounds was further proved by the reaction of benzoxazole **2.10** (R=CH_3) with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and triethylamine, using a procedure by Crociani *et al*.,[8] to form a palladium allyl complex with the benzoxazole. Within an hour after addition of the reagents, Pd(0) leached out of the reaction and the thin layer chromatography analysis revealed only the starting ligand.

With the different crystal structures in hand the characterisation data was re-examined to try and determine which of the crystal structures were the product that was returned after the synthesis of the compounds and by what possible route. The possibility existed that the di-acetate complex could be the main product, but due to the recrystallization process (warming the solutions, long periods in solution) could form into the dinuclear product as seen for the crystal structures of **2.10b** and **2.11b**. Other possibilities that also existed were that the products were recovered as a mixture of the mono- and dinuclear products. If the mononuclear products had the same dissociation character as the $[PdCl_2\mathbf{L}_2]$ it would explain why signals that corresponds to the starting ligands could be found in the NMR spectra and only the m/z value for the dinuclear complexes in the mass spectrum of the complexes. A ^{1}H

NMR spectrum was also acquired of $Pd(OAc)_2$ in deuterated dimethylsulfoxide and the sample revealed that there was a broad signal near 1.80 ppm as well as a small signal near 12 ppm. These signals corresponded in position to the signals that seen in most of the spectra, but was not an explicit indication that the signals could originate from excess $Pd(OAc)_2$.

The most important reaction to study was the reaction of phenylbenzoxazole **2.9** with $Pd(OAc)_2$ under different conditions, due to the opposing conclusions that were drawn from the data. Characterisation data in this regard was complicated by the exact resemblance of the ^{1}H NMR spectra of the precipitate of the concentrated reaction, performed over three hours, and the product recovered from the diluted reaction, performed overnight. The product that was recovered overnight was also used to perform the mass spectrum analysis that returned the mass resembling the dinuclear product. It was thus reasoned that the precipitate and the product recovered from the diluted reaction were the same, both being the dinuclear complex. This would explain the disappearance of the O-H vibration in the FT-IR spectrum, but not the vibrations that could be assigned to the CO_2^- stretches. Another possibility that had to be taken into account is that the samples were mixtures of the mono- and dinuclear complexes, as stated above. Benzoxazole complex **2.10b** also produced this situation as described for **2.9b**.

For complex **2.11b** and **2.13b** the situation was different. FT-IR and ^{1}H NMR spectroscopy of **2.11b** did show that there was a possibility that there were a mixture of two products. **2.13b** on the other hand showed only the presence of one product. To make sure this was the case two equivalents of triethylamine were added to a reaction of ligand **2.13** (R=H) with $Pd(OAc)_2$ in dichloromethane, also resulting in the immediate precipitation of an orange product. FT-IR spectroscopy of the solid revealed that it was an exact match to the spectrum recorded for the reaction without the addition of triethylamine, concluding that the dimetallic complex **II** was formed as the only product.

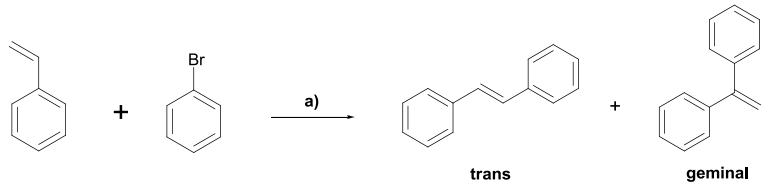
From the characterisation data that was collected it became apparent that the formation of the coordination compounds of the benzoxazole ligands with $Pd(OAc)_2$ depended greatly on the benzoxazole itself. It appeared as if the reactions with **2.9** (R=Ph) and **2.10** ($R=CH_3$) proceeded in the same manner and that **2.11** (R=Bn) and **2.13** (R=H) had much in common and that the formation of the metallocycle compound would probably not be possible with these ligands.

Using the data and compounds at hand it was decided to investigate if these compounds would be able to be used as C-C forming catalyst.

3.3 Catalysis

To satisfy our curiosity it was decided to look at the possible C-C bond formation capabilities of the compounds that were made, by using the Heck reaction. It was decided to couple styrene and bromobenzene, in dimethylformamide, as a model reaction and only look at the effect of time and different bases on the reaction profile.

Table 3.12 Results from the testing of **2.10a** in Heck catalysis. Reagents and Conditions: a) bromobenzene (2 mmol), styrene (2.5 mmol), base (4 mmol), **2.10a**, DMF, reflux.



Run	2.10a (mol%)	Base	Time (h)	Yield (%)[a]
1	2	Et_3N	19	11
2	2	NaOAc	19	14
3	1	NaOAc	20	17
4	0.6	NaOAc	20	12
5[b]	1	NaOAc	20	15
6	1	NaOAc	93	33

[a] Combined isolated yield, [b] Degassed

An initial reaction of methylbenzoxazole **2.10** and $PdCl_2$ did not show great promise, with Pd black forming quite early on in the reaction, and it was decided to use the complexes as catalyst in the next reactions. This allowed for easier handling and it was presumed that it would be more stable starting material for the reaction. In Table 3.12 the data gathered from the different reactions can be viewed. The reaction was performed as follows: The coordination complex was dissolved in dimethylformamide and the base added. This mixture

was stirred, after which the bromobenzene and styrene added and the reaction warmed to reflux for the required time. After work-up the product was collected by column chromatography. When the reactions were repeated with iodobenzene, leaving it to reflux for 23 hours, it was discovered that the reactions went to completion, returning yields > 90%. To verify the results the Heck reaction was repeated with iodobenzene, returning the same yield. This was also seen when some of the other $PdCl_2$-complexes were used, pointing to some possible contamination of the bromobenzene.

The reactions were studied on a smaller scale (using GC-MS and an internal standard to calculate the conversion of iodobenzene, see Table 3.13) and it was revealed that all the reactions were complete after 23 hours, the only exception when **2.12a** was used as precursor (95% conversion).

Table 3.13 Results from the testing of Pd complexes in Heck catalysis. *Reagents and Conditions*: a) iodobenzene (1 mmol), styrene (1.5 mmol), Et_3N (1 mmol), 1 mol% complex[a], DMF, 120 °C, 23 hours.

Run	Complex[a]	Conversion (%)[b]	Ratio of Product Isomers[b] (geminal:trans)
1	**2.9a**	100	11:89
2	**2.10a**	100	13:87
3	**2.11a**	100	12:88
4	**2.12a**	95	12:88
5	**2.13a**	100	12:88

[b] Determined by GC-MS, calibration based on *p*-xylene.

What was of more interest was that the ratio of the *geminal* to *trans* products (see Table 3.12 for the products from the reaction) was formed in about 1:8. It was speculated that the increase in size of the substituent on the 2-position, and the use of a neutral Pd complex,[40, 41] would mean more of the *trans*-stilbene would be formed. However, when only $PdCl_2$ was used under the same conditions the conversion of the reaction was also 100% with a similar ratio of products formed. This pointed to the possibility that the ligand did not play a role in the catalysis and the formation of the products was solely due to the reaction of the substrates with the palladium salt. From literature it also became clear that the conditions used were too harsh and it probably lead to the decomposition of the complexes and the

formation of a heterogeneous catalyst system or at least ligand-stabilised metal colloids.[42, 43] Cabri and co-workers also pointed out that aryl iodides do not need a ligand stabilised Pd species to assist with the initial oxidative addition step of the Heck reaction, but when using another substrate it is quite important.[40, 41] The lack of a ligand stabilised Pd(0) species could also explain why the Heck reaction of **2.10a** with bromobenzene gave such low combined yields in our hands and strengthened the case that the ligand played little or no influence in the reactions. In hindsight the results should have been expected due to the dissociative nature of the $PdCl_2$ complexes and their general decomposition under high temperature and polar solvents.

The focus now turned to the synthesis and coordination chemistry of P(III) functionalised benzoxazoles.

3.4 References

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CHAPTER 4

Functionalisation of Benzoxazoles

4.1 Introduction

In Chapter 3 the coordination chemistry of the 4-hydroxybenzoxazole ligands **2.9-2.13** were examined using Pd(II) salts. Our attention was now turned to broadening the ligand library by functionalising the phenol group to impart different ligand donors (N, P, OR, N see Figure 4.1) as this was the most logical starting point. It was foreseen that the different ligand donors would cause the molecules to act as hemi-labile ligands, a topic that is of great interest in coordination chemistry.[1]

Figure 4.1 Example of the further functionalization of the benzoxazole scaffold (R = H, Me, Ph etc.; $R^1 = PR_2$, alkyl)

Inspiration for this work was drawn from an article of Kallstrom *et al*.,[2] (Figure 4.2**A**) on the iridium-catalysed asymmetric hydrogenation of olefins utilising phosphinite-oxazoles as ligands. These and other (benz)azole ligands (Figure 4.2**B**) were also used in their collaborative research on other asymmetric induction reactions (intramolecular asymmetric Heck reaction, allylic alkylations).[3, 4] The compounds exhibited a close relationship to the benzoxazole ligands that were synthesised in this study and it was decided to investigate if it was possible to synthesise ligands with a phosphorous moiety on the phenol group of the 4-hydroxybenzoxazoles. Scrutiny of the literature found only one reference for 4-hydroxybenzoxazoles with phosphorous groups directly attached to the phenol (Figure 4.2**C**).[5]

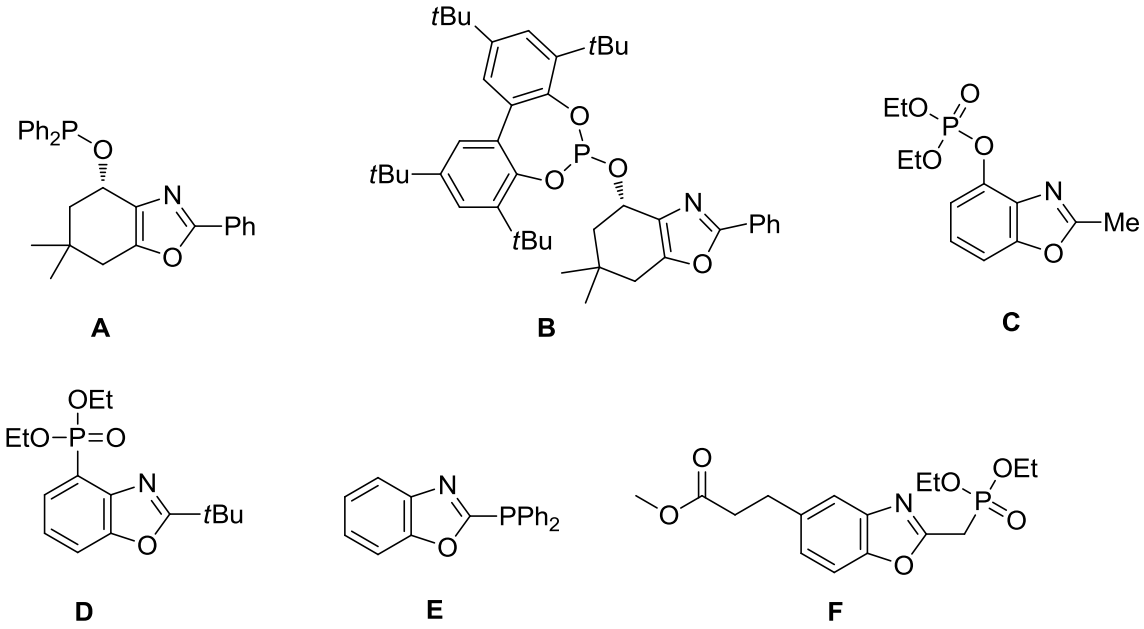


Figure 4.2 Examples of (benz)oxazoles with phosphorous functionalities

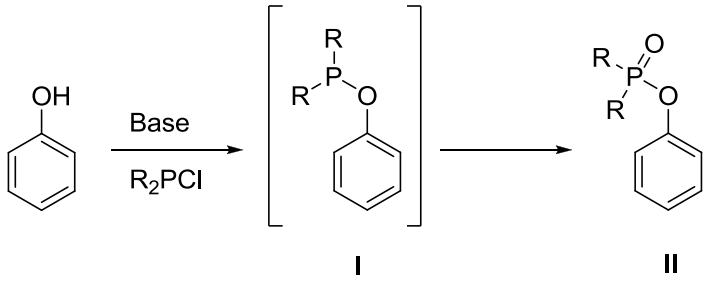
Further examination of the literature led to examples where the phosphorous groups were attached to the 4- or 7-position of the aromatic ring (Figure 4.2**D**)[6-9] or to the 2-position of the oxazole ring, directly (Figure 4.2**E**)[10] or via a –CH_2- linker. The latter case has been reported as a substrate for Horner-Wadsworth-Emmons olefination (Figure 4.2**F**)[11] or used as a ligand.[12, 13]

4.2 Attempts to synthesise phosphine derivatives

4.2.1 Direct methods

Literature presented a variety of methods to synthesise phosphinite **I** (Scheme 4.1) from phenol groups, with some representative samples mentioned.[2, 14-18] In general all of the methods entailed the use of a base (e.g. sodium hydride, *n*-butyllithium, triethylamine etc.) and a suitable phosphine chloride. These compounds are generally very unstable and tend to oxidise *in situ* to the phosphinate **II** (Scheme 4.1), making purification of the phosphinite very difficult. In most of the cases in the literature minimal purification was performed on the compounds and they were used as is in the next reaction.

For the synthesis of the benzoxazole phosphites it was decided to find a general method. In this manner the compounds can all be produced under the same conditions, thus making the production of a wide range of ligands possible.



I II

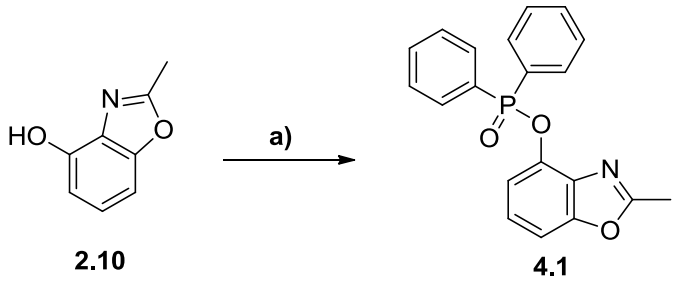
Scheme 4.1 Representative example of the synthesis of phosphinite **I**. The phosphinate **II** can be easily formed *in situ*. (R = alkyl, aromatic).

The first method that was attempted was an adapted method from Kallstrom *et al*.[2] Methylbenzoxazole **2.10** was dissolved in tetrahydrofuran and cooled to −78 °C. To the mixture was added 1.2 equivalents of *n*-butyllithium and the colour of the clear solution changed to yellow. The yellow-coloured solution was left to stir for five minutes, after which it was allowed to warm to room temperature and left to stir for a further 30 minutes. To the brownish reaction were added 1.1 equivalents of diphenylphosphine chloride. The reaction initially turned back to yellow and was left to stir at room temperature overnight. Thin layer chromatography revealed that the reaction did not go to completion and it was decided to remove the solvent *in vacuo* to investigate the two newly formed polar products. Column chromatography on silica gel returned more than 80% of the starting material and only a small amount of polar compounds. It was assumed that the deprotonation of the phenol with the lithium base needed more time and in a follow up reaction the base was left to stir with the ligand for two hours at room temperature. The rest of the reaction was followed as previously mentioned. Thin layer chromatography revealed two new non-polar products, predicted to be the phosphinite and some excess phosphine chloride, as well as a large quantity of starting material and the polar products. Chromatography again returned more than 80% starting material and only the two polar products in very small amounts. It was thought that the phosphinite probably formed in the reaction, but was oxidised either during the filtration or during the chromatography.

It was decided not to pursue this method any further, since it also came to our attention that the reaction between benzoxazole **2.13** (R=H) and *n*-butyllithium was used to generate isonitrile ligands and would thus not lead to a general method for the synthesis of the compounds. [19-21]

The next synthesis route that was looked at was the use of triethylamine in toluene at room temperature (see Scheme 4.2).[14, 22] Methylbenzoxazole **2.10** was dissolved in toluene and

1.5 equivalents of triethylamine were added to the solution. After five minutes one equivalent of diphenylphosphine chloride was added dropwise to the solution and a white precipitate, presumably triethylamine hydrochloride, formed. After 19 hours stirring at room temperature the benzoxazole **2.10** was not consumed according to thin layer chromatography and it was decided to leave the reaction longer. Again a non-polar product was forming, but as the reaction progressed the product slowly disappeared and the polar products increased. The reaction was tested at regular intervals and after 50 hours no further change had occurred and the reaction was filtered through Celite and washed with toluene. Removal of the solvent, followed by column chromatography produced the starting material as well as a new product.



2.10 **4.1**

Scheme 4.2 Synthesis of phosphinate **4.1**. *Reagents and reaction conditions*: a) i) Et_3N (1.5 equiv.), toluene, rt. ii) PPh_2Cl (1 equiv.), rt.

^{31}P NMR spectroscopy of the compound revealed a signal at 32.6 ppm. This confirmed that the phosphinate had formed and not the expected phosphinite. The phosphinate **4.1** was thus returned in a yield of 32%. These reactions were also repeated by warming the mixtures to reflux in an effort to drive the reaction to completion.[15, 23] The first reaction was kept for 22 hours and returned only 10% of **4.1**, while a reaction that was allowed to reflux for 72 hours returned only 30% of **4.1**. At this point the direction of the study changed somewhat. Up to now all the reactions returned large percentages of unreacted starting material and it was decided to first focus on finding a method to drive the reaction to completion, even if the phosphinate was formed.

As one of the first options it was decided to look at the use of another irreversible base, sodium hydride, as was used by Crociani *et al*.[16] in their synthesis of phosphinite quinoline-derivatives. To 1.2 equivalents of the base in tetrahydrofuran was added a tetrahydrofuran solution of methylbenzoxazole **2.10**. The reaction mixture was warmed to reflux for one hour to aid the deprotonation of the compound, allowed to cool to room temperature. The phosphine chloride was added to the solution and the mixture was again warmed to room

temperature and left overnight. Work-up of the reaction consisted of filtration over basic alumina followed by column chromatography to return the phosphinate in 41% yield. This reaction was also repeated using benzoxazole **2.13** (R=H) in an effort to gauge if the benzoxazole was a problem. The reaction returned about 50% of benzoxazole **2.13** as well as two new products. ^{31}P and ^{1}H NMR spectroscopy of a crude reaction sample revealed the existence of the phosphinate product, albeit in about 20% yield.

Klausmeyer mentioned that five physical aspects played a big role in the synthesis of their phosphinite ligands. They found that heat, light, rate of addition,[17, 24] concentration and the type of solvent all played a part in the formation of by-products, especially the formation of a phosphine/phosphine-oxide [$PPh_2P(O)Ph_2$] by-product.[14] From the data at hand it was decided to focus on reactions that did not need high temperatures, since it was clear that these reactions could provide extra problems to an already difficult task.

Table 4.1 Summary of some of the conditions employed in the synthesis of phosphinate **4.1** (see Scheme 4.2).

Base	Solvent	Conditions	Time (h)	Yield (%)
*n*BuLi	THF	− 78° → rt	0.5/o.n.	< 10
Et_3N	Toluene	rt	50	32
Et_3N	Toluene	reflux	21	10
Et_3N	Toluene	reflux	72	30
NaH	THF	reflux	1/23	41
Et_3N	THF	−40° → rt	0.5/20	60

An adapted method by Uemura and co-workers proved to return the best results.[17, 24] The methylbenzoxazole **2.10** was dissolved in tetrahydrofuran and cooled to −40 °C. To this solution was added 1.5 equivalents of triethylamine and the reaction was stirred for a further 15 minutes. Then a solution of the phosphine chloride in tetrahydrofuran was added drop-wise to the reaction and a white precipitate formed immediately. The mixture was stirred for

10 minutes after which it was allowed to warm to room temperature and left to stir for 22 hours. Thin layer chromatography after two hours at room temperature revealed the formation of the non-polar product and this was still visible after 22 hours, but again the starting material was not consumed. Even after careful filtering and column chromatography only the phosphinate **4.1** was recovered in 60% yield. The rest of the material was the starting compound **2.10**. This was the best result so far and the reaction was investigated in more detail. Follow-up reactions returned low yields and it was found that the state of the phosphine chloride had deteriorated considerably. Using a new bottle of reagent returned repeatable results.

Reactions started at −10 °C or even at 0 °C also returned similar reaction profiles, but still some starting benzoxazole remained unreacted. Lal *et al*.[25] reported in their synthesis of phosphinite ligands that it was crucial to add *N*,*N*-dimethylamino pyridine (DMAP) to their reaction in order to achieve full conversion to the required product. Repeating our reaction and adding 10 mol% of DMAP as additive caused the reactions to achieve full conversion within four to six hours. It was noticed during chromatography that again a large quantity of the starting material **2.10** (R=CH_3) was returned. Close inspection of the thin layer chromatography plates used revealed that the product was decomposing during chromatography. It is known that the phosphinite groups can be easily hydrolysed by solvents/moisture and it was reasoned that the polar silica gel used as stationary phase was responsible for the decomposition of the product. When thin layer chromatography of the reaction was run on an alumina plate it was observed that the product appeared more stable. Thus switching to alumina as stationary phase and performing the separations over short plugs rectified the problem to a certain extent. Using more equivalents of DMAP (20-30 mol%) did increase the rate of the reaction (as followed by thin layer chromatography). Using only one equivalent of DMAP, i.e. acting as transfer agent and base, was not successful, but when triethylamine was added the reaction was completed in less than 15 minutes. The yield of the reaction after purification did however not increase.

At this point a few characteristics of the reactions and their products became clear. The phosphinite moiety was successfully formed in the reactions, but the compounds were very susceptible to oxidation (even if the greatest care was taken with the reactions, work-up and purification) or hydrolysis which caused it to form the phosphinate or the starting benzoxazole respectively. All the phosphinate compounds were recovered after chromatography as colourless, gummy semi-solids that hardened over time and were stable as the solid, but did decompose slowly in solution.

Phosphinate **4.1** was recrystallized by the diffusion of petroleum ether into a concentrated dichloromethane solution of the benzoxazole with subsequent evaporation at room temperature. In the process a suitable single crystal was recovered and analysed using X-ray diffraction crystallography.[26] **4.1** crystallised in the orthorhombic space group *Pbca* and the asymmetric unit consist of only the one molecule of the phosphinate. Figure 4.3 displays a perspective view of the asymmetric unit of **4.1**, together with the labelling scheme used in the structural analysis.

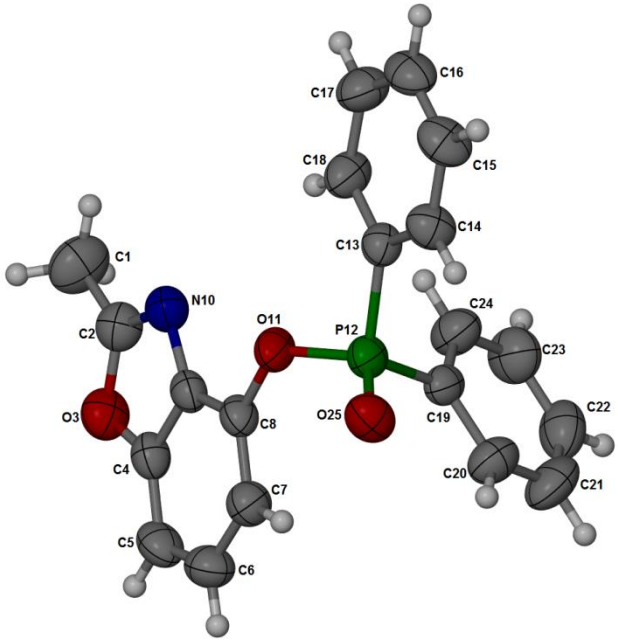


Figure 4.3 Molecular structure of benzoxazole phosphinate **4.1** with the labeling scheme. All non-hydrogen atoms are drawn as displacement ellipsoids at 50 % probability and H atoms are shown as spheres of arbitrary radius.

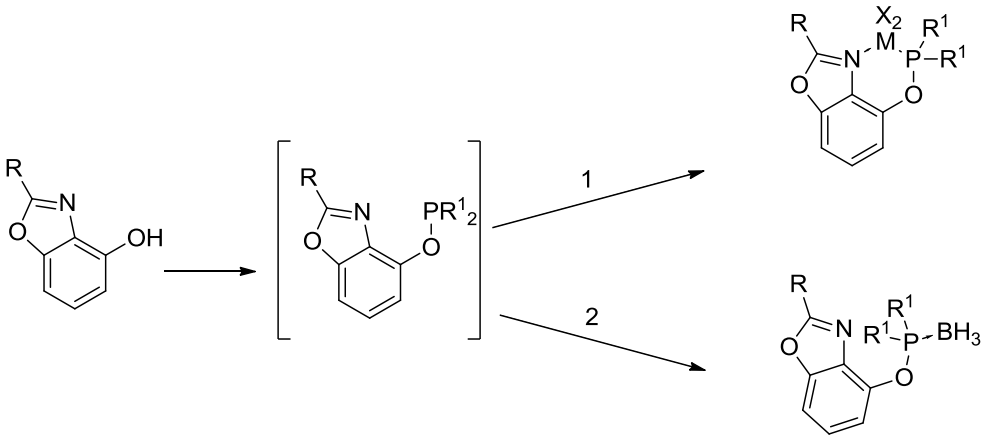
In the molecular structure of the compound the almost planar benzoxazole moiety was attached to the slightly distorted P12 [99.36(8)° - 115.37(8)°] atom through O11. All the bond lengths are within normal values and Table 4.2 contains a summary of some selected bond lengths and angles. The crystal structure of **4.1** is stabilised by weak intermolecular close contact interactions. The C-H···π interaction of the molecule with a centro-symmetrically related molecule [C22···centroid of 6-membered ring (C13-C18) = 3.577(3) Å] appears to be the most dominant force. The molecules are further interconnected by a weaker C-H···π interaction between two adjacent molecules [C1···centroid of 5-membered ring of benzoxazole = 3.819(3) Å].

Table 4.2 Selected bond lengths (Å) and angles (°) for **4.1**. Numbering can be seen in Figure 4.3.

P12-C13	1.785(2)	P12-O11	1.6075(14)
P12-C19	1.786(2)	P12-O25	1.4665(15)
N10-C2	1.291(3)	O11-C8	1.392(2)
C13-P12-C19	109.59(9)	O11-P12-C13	99.36(8)
O25-P12-C13	113.91(9)	O11-P12-C19	104.76(8)
O25-P12-O11	115.37(8)	O25-P12-C19	112.73(9)

4.2.2 In situ trapping and protection of the phosphinite

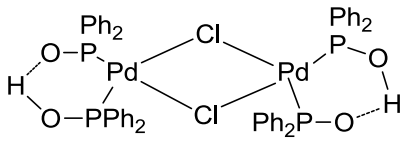
Careful scrutiny of the literature revealed two possible *in situ* methods, used in other ligand systems, to overcome the problem of purifying the phosphinite (Scheme 4.3). The first is the formation of a coordination complex with a Pd-salt, as reported by Cook *et al*.[27] The main advantage of this method would be the formation of the coordination complex in one step. The second method was the protection of the formed phosphinite as a borane adduct (Scheme 4.3).[28, 29] Both of these methods allowed for the purification of the stable complexes and in the case of the second method the borane can be removed using well established methods and the product used in further reactions steps.[28, 30, 31]



Scheme 4.3 Formation and *in situ* phosphinite protection strategies. 1: Protection as the coordination complex. 2: Protection as the borane adduct. (R, R^1 = aryl or alkyl, MX_2 = metal salt)

Benzoxazole **2.10** (Scheme 4.3, route 1) was treated with the DMAP adapted method and after four hours one equivalent of $[PdCl_2(MeCN)_2]$ in dichloromethane was added to the reaction and it was left to stir overnight. Thin layer chromatographic analysis revealed the disappearance of the intermediate phosphinite, thus the orange reaction mixture was filtered through Celite and the solvent removed. The crude reaction mixture was treated with dichloromethane and hexane and a yellow precipitate formed. This was collected and ^{1}H NMR spectroscopic analysis revealed that the product did not contain any recognisable patterns associated with the methylbenzoxazole **2.10**, but rather aromatic protons and a single signal at about 78 ppm in the ^{31}P NMR spectrum. The reaction was repeated, this time leaving the metal to react with the intermediate for two hours, only to return the same result.

While investigating some chemical transformations on phosphorous ligands we came upon work performed by Balakrishna *et al.*[32] describing a chloro-bridged binuclear complex $[\{Pd(\mu\text{-}Cl)(PPh_2O)(PPh_2OH)\}_2]$ **4.2** (Figure 4.4) formed after complexation of a Pd-precursor to their phosphinite ligand. Their investigation pointed to a possible moisture assisted P-O bond cleavage being responsible for the end result. The analytical data (^{1}H NMR spectroscopy and melting point) of the precipitate corresponded with Balakrishna's binuclear product and was thus assigned as **4.2**. Further attempts at using the other 4-hydroxybenzoxazoles returned the same result.



4.2

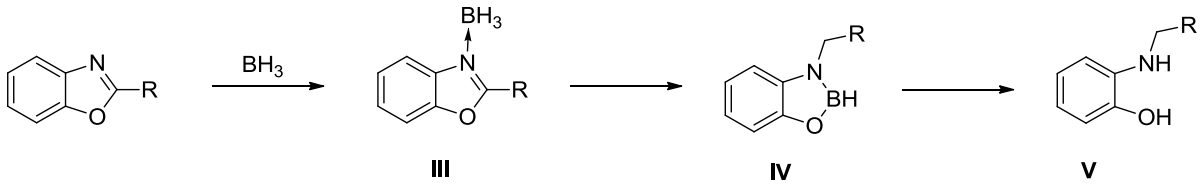
Figure 4.4 Chloro-bridged binuclear complex $[\{Pd(\mu\text{-}Cl)(PPh_2O)(PPh_2OH)\}_2]$ **4.2.**

The ability of the phosphinite to form rearranged products during coordination to other transition metals was also supported by other publications.[33-35] In most of the cases this was due to adventitious moisture in the reaction setup or it was solvent directed. What was very interesting about **4.2** and its derivatives was that they were used as catalysts in C-C forming reactions to good effect.[36-40] This reaction was also repeated with $Pd(OAc)_2$, but the reaction only returned a dark brown/black residue that was only soluble in sulphuric acid.

Using the second method also failed to solve the problem (Scheme 4.3, route 2). After forming the intermediate phosphinite, the reaction was treated with two equivalents of BH_3 in tetrahydrofuran (1M solution). A complicated mixture of products formed that could not be

fully separated using column chromatography. Although a small amount of the protected benzoxazole was formed (<20%), it became clear that the borane was also reacting with the benzoxazole itself. This was confirmed by adding two equivalents of BH_3 in tetrahydrofuran (1M solution) to a solution of benzoxazole **2.13** in tetrahydrofuran. Thin layer chromatographic analysis of the reaction revealed a multitude of products. Attempts to purify the reaction were not successful due to further decomposition on the silica and also on alumina.

It was found in the literature that benzoxazole derivatives and borane readily form stable adducts **III** (Scheme 4.4). These compounds can undergo rearrangements to form benzoxaboroles **IV** and the ring-opened amines **V** according to the conditions they are subjected to, of which the most notable are high reaction temperatures and treatment with aqueous acids.[41, 42] **V** can also be synthesised directly from the benzoxazole, by treating it with common reducing agents.[43]



Scheme 4.4 Example of the products formed from the treatment of benzoxazoles with borane and the rearrangement products (R = alkyl, aryl etc.).

The failure to synthesise the phosphorous derivatives of the benzoxazoles meant that a large part of the study aims would not be realised. However the question would always have been that if we were successful and catalysis was possible, what would have been the reactive species? Would the benzoxazle moiety have played any role or would it simply be the binuclear **4.2** that would have been responsible for the reactivity?

From here it was decided to focus on developing a method of synthesising the chiral derivatives.

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CHAPTER 5

Synthesis of Chiral Benzoxazoles

5.1 Introduction

As part of our study it was envisioned to synthesise chiral derivatives of 4-hydroxybenzoxazoles, making use of amino acids (see Figure 5.1). To develop the synthetic method a small library of benzoxazoles with 2-aminophenol would be synthesised with six L-amino acids (glycine, alanine, valine, leucine, phenylalanine and proline). The amino acids were chosen according to two criteria: All are carbon based side chains of varying degrees of bulkiness and all of them, except glycine, have only one centre of stereochemistry on the α-carbon. The process would then be repeated to synthesise a library using 2-aminoresorcinol **2.2**.

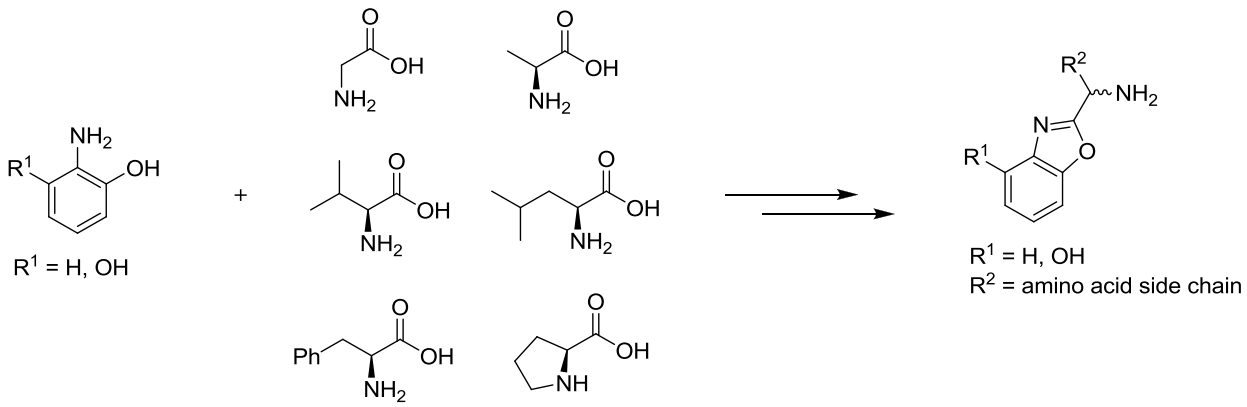


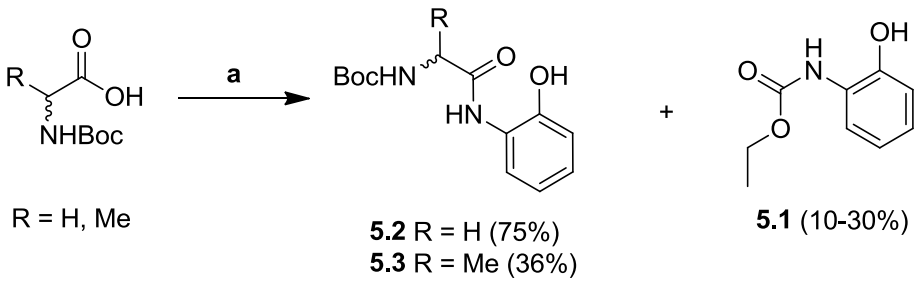
Figure 5.1 The target benzoxazole library

5.2 Synthesis of Asymmetric Benzoxazoles

5.2.1 Aminophenol benzoxazole derivatives

The first step in the synthesis was to find a suitable method of forming the amide bond, since there are a large amount of methods available.[1, 2] The formation and the use of the amino acid acyl chloride to provide the amide, as was used in Chapter 2, provided a too great a risk for the racemisation of the compounds and it was decided to look for an alternative method.

The first method investigated was the forming of a mixed anhydride between ethyl chloroformate and an *N*-Boc-protected amino acid in tetrahydrofuran and triethylamine, and subsequent reaction with 2-aminophenol at 0 °C (see Scheme 5.1).[3, 4] The reaction was warmed to room temperature and left to stir overnight, followed by an acidic aqueous work-up and purification by column chromatography. Initial results, using *N*-Boc-glycine, revealed the formation of two products, the Boc-protected amide **5.2** and ethyl 2-hydroxyphenylcarbamate **5.1** in 53% and 22% yield respectably. Repeating the procedure with Boc-*N*-L-alanine returned the Boc-protected amide **5.3** and carbamate **5.1** in 36% and 30% yield respectively. The closely matching polarity of these compounds made purification really difficult to perform with column chromatography. The reaction with Boc-*N*-glycine was attempted again with some minor adjustments: the formation of the anhydride was given more time (one hour vs 30 minutes), slower warming to room temperature and longer reaction time (60 hours vs 20 hours) returned a yield of 75% for **5.2** and only 10% for **5.1**. Although a vast improvement in yield was experienced, it was foreseen that purification problems would arise when other amino acids would be used and this method was not pursued further.



Scheme 5.1 Synthesis of Boc-protected amides **5.2** and **5.3**. *Reagents and reaction conditions*: a) i) EtO(O)Cl (1 equiv.), Et_3N (2 equiv.), THF, 0 °C. ii) 2-aminophenol (1.2 equiv.), 0 °C→rt.

There are a number of methods reported in the literature to perform amide couplings on the aminophenol systems. From this three main approaches could be seen:

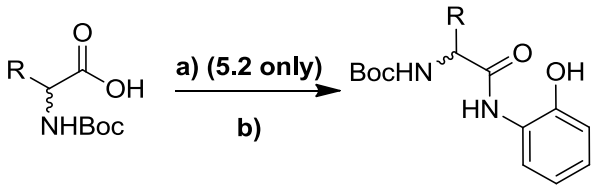
1) Using HATU (2-[1*H*-7-Azabenzotriazol-1-yl]--1,1,3,3-tetramethyl uronium hexafluoro-phosphate Methanaminium) as coupling reagent.[5-7]

2) Making use of DCC (*N,N'*-Dicyclohexylcarbodiimide) as coupling reagent.[8, 9]

3) Using EDC·HCl (1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride)[10-13] with either DMAP (4-Dimethylaminopyridine) or HOBt (1-Hydroxybenzotriazole) to increase the reaction rate and decrease racemisation of the coupling reaction.

All of the conditions mentioned in the articles were tested and although most of these methods worked very well some problems were surfacing. In the case of the HATU method an excess of three equivalents of the coupling reagent was needed to perform the reaction, which seemed wasteful and the DCC method gave too many problems with the purification of the desired amide, due to the formation of the DCC-urea by-product. Regardless of these problems, moderate yields were recovered for both reactions.

Table 5.1 Synthesis of the functionalised aminophenol amides **5.2-5.7**. *Reagents and reaction conditions*: a) 2-aminoresorcinol (1 equiv.), DCC (1equiv.), MeCN, rt b) 2-aminophenol (1.05 equiv.), Et_3N (2 equiv.), EDC·HCl (1.05 equiv.), HOBt (1.05 equiv.), DCM, rt.



5.2-5.7

Product	R (L-Amino Acid)	Yield % (based on acid)	$[\alpha]_D$
5.2	H (glycine)	90	n/a
5.3	Me (alanine)	56	-101.6 (*c* 0.40, $CHCl_3$)
5.4	CH_2Ph (phenylalanine)	70	- 22.0 (*c* 0.09, $CHCl_3$)
5.5	$CH(CH_3)_2$ (valine)	50	- 43.8 (*c* 0.14, $CHCl_3$)
5.6	$CH_2CH(CH_3)_2$ (leucine)	60	- 55.6 (*c* 0.09, $CHCl_3$)
5.7	C_4H_8N (proline)	77	- 148.9 (*c* 0.40, $CHCl_3$)

It was found that the best yields were recovered using an EDC·HCl and HOBt method by Carotti *et al*.[10] (see Table 5.1). The first reactions were started at 0 °C, but it was found that

less of the di-acylated products were formed if the reaction was performed at room temperature. Careful and very slow chromatography was needed to separate the products and in most cases these were inseparable mixtures. A literature survey revealed the use of lithium hydroxide as a very mild agent for ester hydrolyses, [14] and it was decided to test this on the compounds as a way to ease the separation of products from by-products. After the initial amide coupling reaction work-up the solids were re-dissolved in tetrahydrofuran and treated with a solution of three equivalents of lithium hydroxide monohydrate in a 1:1 mixture of water and tetrahydrofuran at ambient temperatures. The reaction was monitored with thin layer chromatograph until completion and after an acidic aqueous work-up the product was purified by column chromatography. In all of the cases the reactions were left to stir at room temperature for 18-24 hours, showing almost no differences in yield if left for longer. For the coupling reaction with *N*-Boc-glycine the yield that was recovered when using the different methods did not differ greatly and it was decided to perform the reaction with DMAP or DCC later in the study.

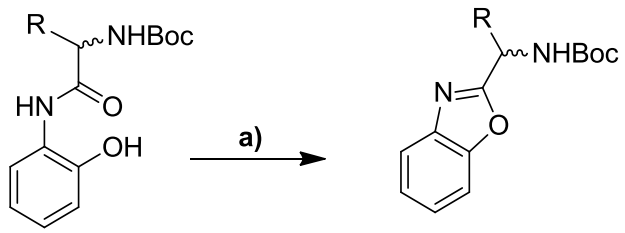
With these products (**5.2**-**5.7**) in hand it was decided to form the corresponding benzoxazoles using our standard method (catalytic or equimolar PPTSA, toluene, reflux). In most cases there was no product formation and large amount of decomposition products were observed using thin layer chromatography. Other methods where heat (microwave heating) and/or acid catalysts (glacial acetic acid, also as solvent) were used, only lead to the abovementioned result. The strong acidic conditions possibly lead to the formation of the very polar products through the decomposition of the starting amides, via the removal of the Boc-group, and the formation of protonated amines. These could in turn hinder the formation of the benzoxazole ring.

This prompted us to look at an alternative, milder route and literature revealed that the Mitsunobu reaction had been used in some cases to form oxazoles and benzoxazoles.[15-18] One encouraging characteristic of this method was that the reactions were performed under ambient temperature, reducing the risk of possible racemisation.

Amide **5.2** and triphenylphosphine, in dry tetrahydrofuran at 0 °C, was treated dropwise with di-isopropyl azodicarboxylate (DIAD) and the solution was slowly warmed to room temperature (see Table 5.2). The reaction was monitored with thin layer chromatography until completion (24 hours) and the product was purified by column chromatography. ^{1}H NMR spectroscopy revealed that the benzoxazole **5.8** was successfully synthesised in a good yield of 85%. This method was applied on amides **5.3**, **5.5** and **5.6** as well, returning yields between 85-90% after 24-26 hours. In the case of the phenylalanine amide **5.4** the

reaction was very slow (additional reagents were added after 48 hours) and it was completed after 100 hours. This was also the case for the synthesis of the proline derivative **5.13**, from **5.7**, returning a yield of 48% after additional reagents and a longer reaction time (43 hours) was needed to force the reaction to completion. Purification of the products were problematic due to the formation of the reagent by-products (Figure 5. 2). Careful column chromatography and stirring the benzoxazoles in 1-5% diethyl ether/heptane solutions for extended periods proved to be the best way of removing the reagent by-products in some cases.

Table 5.2 Synthesis of benzoxazoles **5.8-5.13** using the Mitsunobu reaction. *Reagents and reaction conditions*: a) i) PPh_3 (1.2 equiv.), THF, 0 °C ii) DIAD (1.2 equiv.), 0 °C→rt.



5.2-5.7 **5.8-5.13**

SM [R]	Product	Yield (%)	$[\alpha]_D$
5.2 [H]	**5.8**	85	n/a
5.3 [Me]	**5.9**	87	–62.7 (*c* 0.42, $CHCl_3$)
5.4 [CH_2Ph]	**5.10**	87	–69.8 (*c* 0.39, $CHCl_3$)
5.5 [$CH(CH_3)_2$]	**5.11**	85	–80.3 (*c* 0.11, $CHCl_3$)
5.6 [$CH_2CH(CH_3)_2$]	**5.12**	90	–66.1 (*c* 0.27, $CHCl_3$)
5.7 [C_4H_8N]	**5.13**	48	–103.7 (*c* 0.14, $CHCl_3$)

During 2012 a paper by Hou *et al.*,[19] detailing the synthesis of racemic benzoxazole compounds and chiral versions, using the same method appeared. This re-enforced our choice of method of synthesising this library even further.

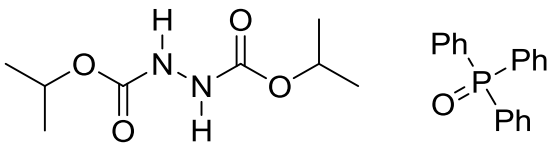
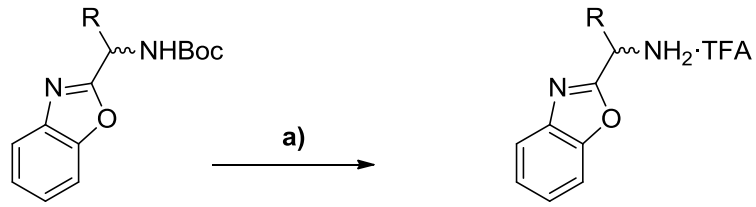


Figure 5. 2 Reagent by-products formed during the Mitsunobu reaction. Left is di-isopropyl hydrazine-1,2-dicarboxylate and right triphenylphosphine oxide.

The last synthesis step was the removal of the Boc protection group using trifluoroacetic acid/dichloromethane (TFA/DCM) to form the corresponding amine salts (Table 5.3). It was found that using 10-15 equivalents of TFA in dichloromethane proceeded to form the purest products, after purification by stirring in diethyl ether/hexane solutions and collecting the white or off-white solids. Frustratingly the phenylalanine derived **5.16** was found to be a racemic mixture after deprotection of the Boc protection group.

Table 5.3 Synthesis of benzoxazoles **5.14-5.19** by *N*-Boc deprotection. *Reagents and reaction conditions*: a) TFA (10-15 equiv.), DCM, rt.



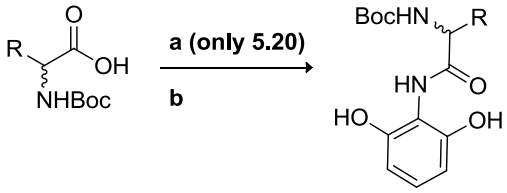
5.8-5.13 **5.14-5.19**

SM [R]	Product	Yield (%)	$[\alpha]_D$
5.8 [H]	**5.14**	80	n/a
5.9 [Me]	**5.15**	77	–19.0 (*c* 0.11, MeOH)
5.10 [CH_2Ph]	**5.16**	77	0 (*c* 0.39, MeOH)
5.11 [$CH(CH_3)_2$]	**5.17**	91	–50.6 (*c* 0.08, MeOH)
5.12 [$CH_2CH(CH_3)_2$]	**5.18**	83	–40.0 (*c* 0.10, MeOH)
5.13 [C_4H_8N]	**5.19**	60	–5.7 (*c* 0.14, MeOH)

5.2.2 Aminoresorcinol derivatives

Our attention was now turned to synthesising the resorcinol amino acid amides (see Table 5.4), from 2-aminoresorcinol **2.2**, using the same procedure as for the synthesis of the aminophenol amides. The only exception was for the synthesis of the glycine **5.20**, since it was decided that the yield for the reaction was sufficient using DCC as coupling reagent.

Table 5.4 Synthesis of the functionalised 2-aminoresorcinol amides **5.20-5.25**. *Reagents and reaction conditions*: a) 2-aminoresorcinol (1 equiv.), DCC (1equiv.), MeCN, rt b) 2-aminoresorcinol (1.2 equiv.), Et_3N (2 equiv.), EDC·HCl (1.05 equiv.), HOBt (1.05 equiv.), DCM or DMF, rt.



5.20-5.25

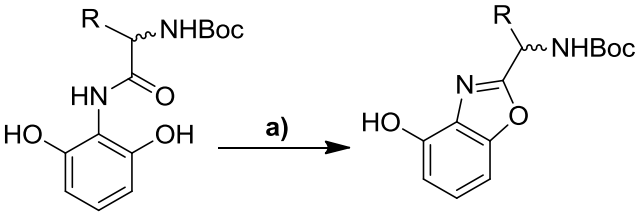
Product	R (Amino Acid)	Yield % (based on acid)	$[\alpha]_D$
5.20	H	80	n/a
5.21	Me	62	–59.6 (*c* 0.50, $CHCl_3$)
5.22	CH_2Ph	70	–27.7 (*c* 0.56, $CHCl_3$)
5.23	$CH(CH_3)_2$	38	–22.2 (*c* 0.14, $CHCl_3$)
5.24	$CH_2CH(CH_3)_2$	62	–58.9 (*c* 0.53, $CHCl_3$)
5.25	C_4H_8N	45	–97.7 (*c* 0.13, $CHCl_3$)

The yields for these products **5.20-5.25** were very low due to the formation of the tri-and di-acetylated coupling products in all the reactions. Careful and very slow chromatography was needed to separate the products and in most cases these were inseparable mixtures. As was the case with the synthesis of **5.3-5.7**, ester hydrolysis with lithium hydroxide proved to

be a valuable method of easing the purification of the products. This resulted in low to good yields for products **5.20-5.25** (38-80%). These reactions were later performed in dimethylformamide as solvent (with or without the base) due to the low solubility of the amine **2.2** in dichloromethane, with no significant change in reaction yields.

In an attempt to synthesise the benzoxazoles from the corresponding amides, using the Mitsunobu reaction, we ran into some problems (see Table 5.5 for numbering). Although the reaction of amide **5.20** to benzoxazole **5.26** progressed as normal the formation of **5.27-5.29** did not proceed very well and returned low yields (<40%). Starting material, reagents and reagent by-products (Figure 5. 2) were mainly recovered as inseparable mixtures. The reactions were very slow (reaction times for all three reactions were 3-5 days) and in the case of **5.28** and **5.29** the reaction was stopped, purified and the starting amide was subjected to another reaction.

Table 5.5 Synthesis of benzoxazoles **5.26-5.31** using the Mitsunobu reaction. *Reagents and reaction conditions*: a) i) PPh_3 (5 equiv.), THF, 0 °C ii) DIAD (5 equiv.), 0 °C→rt.



5.20-5.25 **5.26-5.31**

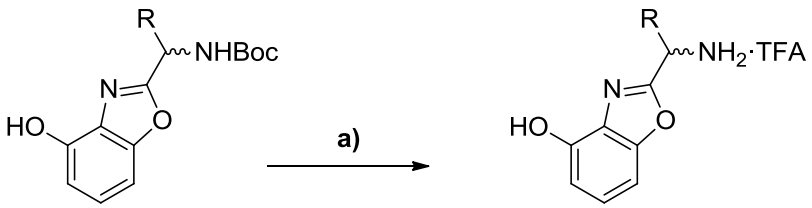
SM [R]	Product	Yield (%)	$[\alpha]_D$
5.20 [H]	**5.26**	85	n/a
5.21 [Me]	**5.27**	60	–106.2 (*c* 0.11, $CHCl_3$)
5.22 [CH_2Ph]	**5.28**	71	–46.7 (*c* 0.11, $CHCl_3$)
5.23 [$CH(CH_3)_2$]	**5.29**	60	–93.2 (*c* 0.12, $CHCl_3$)
5.24 [$CH_2CH(CH_3)_2$]	**5.30**	84	–131.0 (*c* 0.08, $CHCl_3$)
5.25 [C_4H_8N]	**5.31**	64	–120.0 (*c* 0.08, $CHCl_3$)

As with the previous compounds, the Mitsunobu reaction by-products were difficult to separate from the more polar hydroxy-benzoxazoles with column chromatography. Attempts to purify by stirring with solutions of 1-5% diethyl ether/heptane solutions was not as successful as with the other benzoxazole compounds, due again, to the target hydoxy-benzoxazoles and by-products having almost the same polarity.

In some literature cases it was mentioned that the addition of a weak base (Et_3N),[18, 20] the order of addition of the reagents,[20] or an excess of reagents (5-10 times)[15, 20] could force the intramolecular ring closing to completion and return higher yields. The first two suggestions did not help much in this case, but when the ring closing reactions were performed with a five times excess of reagents the products were formed within three hours and generally in higher yields than before. In this manner the benzoxazoles **5.26-5.31** could be synthesised in low to good yields (60-83%, Table 5.5). The use of very dry tetrahydrofuran also facilitated the reaction greatly. It was also discovered that purification of the products was greatly assisted if the column chromatography were performed in mixtures of dichloromethane and ethyl acetate. At low solvent polarities (0-6 % EtOAc/DCM, v/v) the by-products eluted first after which the product could be flushed off at higher solvent polarity (8-20 % EtOAc/DCM, v/v).

The last synthetic step was again the removal of the Boc protecting group using trifluoroacetic acid/dichloromethane (TFA/DCM, Table 5.6). Deprotection using 10-15 equivalents of TFA in dichloromethane proceeded to form the purest products, after purification by stirring in diethyl ether/hexane solutions and collecting the white or off-white solids. Just as in the case with **5.16**, the phenylalanine derivative **5.34** formed a racemic compound after deprotection of the Boc group with TFA. When 4M HCl in dioxane was used to perform the deprotection only decomposition of the starting material could be detected. This gave an indication that the problem was with the amino acid moiety and not the scaffold on which it was synthesised. There was no evidence that could be gathered from the literature that this was a common occurrence and the reason why this was happening is not clear, however the *beta*-phenyl position should not be stabilised by the aromatic ring and thus rendering it easy to racemise.

Table 5.6 Synthesis of benzoxazoles **5.32-5.37** by *N*-Boc deprotection. *Reagents and reaction conditions*: a) TFA (10-15 equiv.), DCM, rt.



5.26-5.31 **5.32-5.37**

SM [R]	Product	Yield (%)	$[\alpha]_D$
5.26 [H]	**5.32**	80	n/a
5.27 [Me]	**5.33**	81	–9.9 (*c* 0.10, MeOH)
5.28 [CH_2Ph]	**5.34**	86	0 (*c* 0.11, MeOH)
5.29 [$CH(CH_3)_2$]	**5.35**	74	–28.3 (*c* 0.11, MeOH)
5.30 [$CH_2CH(CH_3)_2$]	**5.36**	74	–9.5 (*c* 0.11, MeOH)
5.31 [C_4H_8N]	**5.37**	64	–12.9 (*c* 0.16, MeOH)

5.3 Antimicrobial testing*

The final products were then tested against some well-known Gram-positive (*Staphylococcus aureus*) and -negative (*Pseudomonas aeruginosa, Escherichia coli*) bacteria to see if any of them would provide a suitable starting point for further antimicrobial studies. Solutions of the compounds were made up in dimethylsulfoxide to a total volume of 0.2 ml and with concentrations varying from 50-71 mg/ml, the exception being **5.17** (~25 mg/ml). Plate assays were then performed in duplicate (see experimental for details) to screen the compounds' efficacy against the various organisms (see Table 5.7 for results). A

* This was performed with the assistance of the Microbiology Department at Stellenbosch University

sample of TFA was also made up and tested to observe if the TFA would play a role in the compounds efficacy.

Table 5.7 Initial results of the plate assays against the various microbials. X indicates a positive result, - indicates no result. Only when clear results in both plates were observed was it indicated as a positive result.

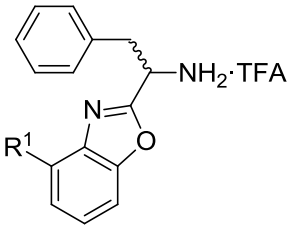
Compound	R	Conc (mg/ml)	*P. aeruginosa* X_{en5}	*E. coli*	*S. aureus*	*S. aureus* X_{en31}
5.14	H	50.3	-	-	-	-
5.15	Me	71.9	-	-	-	-
5.16	CH_2Ph	59.3	X	X	X	X
5.17	$CH(CH_3)_2$	24.9	-	-	-	-
5.18	$CH_2CH(CH_3)_2$	55.1	-	X	X	X
5.19	C_4H_8N	54.9	-	-	-	-
5.32	H	49.7	-	-	-	-
5.33	Me	62.6	-	-	-	-
5.34	CH_2Ph	53.7	-	X	-	-
5.35	$CH(CH_3)_2$	56.3	-	-	-	-
5.36	$CH_2CH(CH_3)_2$	60.2	X	-	X	X
5.37	C_4H_8N	57.3	-	-	-	-
TFA		69.0	X	X	-	-

From these results the following observations could be made:

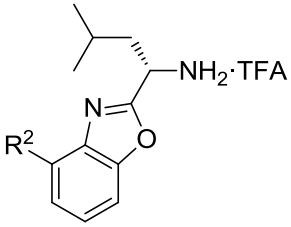
- Very few of the compounds showed any activity
- Compounds with bulky R-groups connected to the benzoxazole scaffold by a $–CH_2$ spacer (**5.16**, **5.34** = benzyl and **5.18**, **5.36** = isopropyl) revealed the most activity, regardless of the benzoxazole scaffold.
- The two racemic phenylalanine compounds also exhibited activity.
- The TFA sample only showed activity towards the Gram-negative bacteria. This however could be due to the free acid and not the salt as is found in the compounds.

Using these initial results it was decided to further test the compounds to get an idea of the concentration ranges were they still would present activity and if the concentrations were low enough, minimum inhibition concentration (MIC) test would be done. Serial dilutions (2x-64x) were made of the compounds **5.16**, **5.34**, **5.18**, **5.36** and TFA, using water as dilution medium, up to a total volume of 0.2 ml (see Table 5.8). Plate assays were then performed again, using the clinical isolates *P. aeruginosa* X_{en5}, *S. aureus* X_{en31} and *E. coli* (see experimental for details).

Table 5.8 Dilution series of the compounds showing activity and the results of the subsequent plate essays on the individual bacterial clinical strains. X indicates a positive result, - indicates no result.



5.16 (R^1 = H)
5.34 (R^1 = OH)



5.18 (R^2 = H)
5.36 (R^2 = OH)

	Dilution Factor and Concentration of Sample (mg/ml)						
Compounds	**1x**	**2x**	**4x**	**8x**	**16x**	**32x**	**64x**
5.16	59.3	29.6	14.8	7.4	3.7	1.9	0.9
5.34	53.7	26.9	13.4	6.7	3.4	1.7	0.8
5.18	55.1	27.6	13.8	6.9	3.4	1.7	0.9
5.36	60.2	30.1	15.0	7.5	3.8	1.9	0.9
TFA	69.0	34.5	17.3	8.6	4.3	2.2	1.1

***P. aeruginosa* X_{en5}**

	Dilution Factor						
Compounds	**1x**	**2x**	**4x**	**8x**	**16x**	**32x**	**64x**
5.16	X	-	-	-	-	-	-
5.36	X	-	-	-	-	-	-
TFA	X	-	-	-	-	-	-

S. aureus X_{en31}

	Dilution Factor						
Compounds	**1x**	**2x**	**4x**	**8x**	**16x**	**32x**	**64x**
5.16	X	X	-	-	-	-	-
5.18	X	-	-	-	-	-	-
5.36	X	-	-	-	-	-	-

E. coli

	Dilution Factor						
Compounds	**1x**	**2x**	**4x**	**8x**	**16x**	**32x**	**64x**
5.16	X	X	-	-	-	-	-
5.34	X	-	-	-	-	-	-
5.18	X	X	-	-	-	-	-
TFA	X	-	-	-	-	-	-

From these results the following observations were made:

- In almost all of the cases there was no indication of activity after the first dilution. It was only **5.16** and **5.18** that showed activity when more diluted (2x dilution), towards *S. aureus* X_{en31} and *E. coli.*
- The TFA did not show any increased activity. This indicated that it did not play any significant role in the activity of the compounds.

Due to the relative high concentrations (60 mg/ml to 15 mg/ml) of activity it was decided not to further test these compounds. These results did however gave an indication of the direction that could be taken for further studies into the antimicrobial activity of these

compounds with the help of in depth molecular modelling studies. Special focus would be on utilising large R-groups with $–CH_2-$ linkers on the 2-position, as well as the functionalisation of the amine group.

5.4 References

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CHAPTER 6

Conclusions and Future Work

6.1 Conclusions

In Chapter 2 the successful synthesis of a range of achiral 4-hydroxybenzoxazoles was demonstrated in good yields. These were formed by making use of amide coupling chemistry and cyclodehydration with pyridinium *para*-toluenesulfonate as catalyst. It was also possible to analyse two of the compounds by single crystal X-ray diffraction analysis.

Making use of the achiral 4-hydroxybenzoxazoles, transition metal complexes could be synthesised from Pd-salts in Chapter 3. Depending on the salt that was used, different coordination modes were displayed by the compounds, resulting in the first recorded structural investigation by single crystal X-ray diffraction analysis of 4-hydroxybenzoxazole complexes. Low solubility and solvent assisted dissociation meant that full characterisation and reaction pathway studies could not be investigated. The $PdCl_2$-benzoxazole complexes were used as catalysts in the Heck reaction. Although they produced good results, it was deduced from the results that the ligands did not play a role in the catalysis.

In Chapter 4 the possible synthesis of P(III) functionalised benzoxazoles and their transition metal complexes was investigated. All attempts to synthesise the phosphinite from diphenylphosphine chloride was unsuccessful and the oxidised product and decomposed material was recovered. An attempt to use *in situ* protection chemistry on the phosphinite, via borane coordination, was unsuccessful and it became apparent that the borane also interacted with the benzoxazole ligand. Another method, trying to trap the phosphinite with a Pd-salt, was also unsuccessful. The formed complex underwent a moisture/solvent re-arrangement to a di-chloride bridged palladium complex, with the oxidised phosphine groups coordinating to the metal centres. These compounds are well known for being good catalyst of C-C forming reactions.

Finally a synthetic route was developed for the synthesis of chiral benzoxazoles and 4-hydroxybenzoxazoles from amino acids. The small library was synthesised using amide coupling chemistry and the oxazole formation was established by the use of the Mitsunobu reaction. The antimicrobial activity of these compounds was also tested against Gram-

positive and –negative microbes. Unfortunately these compounds proved to be not very effective.

6.2 Future Work

Therefore, this project has opened up a wide area of different possible research areas into the synthesis of 4-hydroxybenzoxazoles and their uses, of which a few of these will be mentioned inclosing.

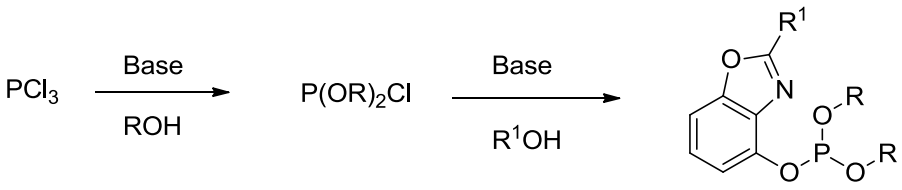
6.2.1 Coordination to other transition metals

The reaction of the library of achiral 4-hydroxybenzoxazoles with other transition metals was also investigated, with limited success. No obvious complex formation could be seen with Ni(II), Pt(II), Cu(II), Cu(I) and Co(II) salts and in most cases the ligand was recovered, but the addition of a base did show that some reaction was taking place. Unfortunately, no products could be gathered from these reactions.

The Zn(II) salts however produced the best results, with and without the use of base. Initial characterisation pointed to the formation of coordination compounds, but again due to low solubility in most organic solvents this could not be fully verified. More work surrounding the use of 4-hydroxybenzoxazoles as ligands is currently ongoing.

6.2.2 Synthesis of other phosphine derivatives

Preliminary work was also done on the possible synthesis of phosphite derivatives of the 4-hydroxybenzoxazoles ligands, due to their higher resistance to oxidation and possible ease of synthesis (Scheme 6.1).[1, 2] At the same time it was also decided to look at the use of other phosphine chloride precursors, to steer away from the use of the problematic diphenylphosphine group. Work on this is currently ongoing.



Scheme 6.1 Synthesis of phosphite benzoxazoles, starting from phosphine trichloride (R = R^1 = alkyl, aryl).

6.2.3 Investigation of the coordination chemistry and uses of the chiral benzoxazoles in catalysis

For a future project it would be interesting to look at the coordination chemistry of the chiral derivatives synthesised in Chapter 5 with commonly used transition metals. These ligands would also then be screened for their possible use in asymmetric catalysis (Ir-hydrogenation,[3] Pd-catalyzed allylic alkylation[4] etc.) as coordination complexes and as possible organocatalysts.[5]

6.3 References

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CHAPTER 7

Experimental

7.1 General Procedures

All chemicals used were bought from Merck or Aldrich. Tetrahydrofuran, pentane, diethyl ether and toluene were dried over sodium wire/sand and distilled under nitrogen with benzophenone as an indicator. Dichloromethane and acetonitrile were distilled over calcium hydride under nitrogen. Other reagents and solvents were purified according to standard procedures.[1]

All reactions were performed under anhydrous conditions in a nitrogen or argon atmosphere, unless stated otherwise. Low temperature reactions were performed in a Dewar using dry ice in acetone (−78 °C), ice in water (0 °C) or a slurry of ethanol, sodium chloride and ice (−20 °C). In the case were precise or long reaction times were needed at low temperature a Julabo FT 401 cooling apparatus was used with acetone or ethanol as cooling liquid. Microwave reactions were performed with a Biotage Initiator microwave reactor.

All ^{1}H, ^{13}C, ^{19}F and ^{31}P nuclear magnetic resonance spectra were obtained using a 300 MHz Varian VNMRS (75 MHz for ^{13}C), a 400 MHz Varian Unity Inova (100 MHz for ^{13}C) and a 300 MHz Bruker Avance-300 (75 MHz for ^{13}C) at Katholieke Universiteit Leuven. The data for ^{13}C and ^{31}P NMR spectra were collected as proton-decoupled. Chloroform-*d* and dimethylsulfoxide-*d6* were used as standard solvents, unless otherwise stated. Chemical shifts (δ) were recorded using the residual chloroform peaks (δ 7.26 in ^{1}H NMR and δ 77.0 in ^{13}C NMR) or the residual DMSO peaks (δ 2.50 in ^{1}H NMR and δ 39.5 in ^{13}C NMR) in DMSO-*d6*, as reference. ^{31}P NMR was referenced to neat H_3PO_4 (δ 0 ppm) and ^{19}F NMR was referenced to $CFCl_3$ (δ 0 ppm). All chemical shifts are reported in ppm and all spectra were obtained at 25 °C, unless otherwise stated.

All chromatography was performed using either (or a combination of) hexane, heptane, ethyl acetate, methanol and dichloromethane. Thin layer chromatography was carried out on aluminium backed Merck silica gel 60 F254 or with PET backed Merck aluminium oxide with a fluorescent indicator (254 nm). Visualization was achieved with an UV lamp, iodine on silica or by spraying with a Cerium Ammonium Molybdate (CAM) or Ninhydrin solution and then heating. Preparative layer chromatography (PLC) was performed on Precoated PLC

Merck silica gel F254 plates. Column chromatography was carried out with Merck silica gel 60 (particle size 0.040-0.063 mm) or with Riedel de Haen aluminium oxide (chromatography grade).

Melting points were obtained using a Gallenkamp Melting Point Apparatus and are uncorrected. Infrared spectra were obtained using a Nexus Thermo-Nicolet FT-IR instrument using the ATR adapter. Optical rotation was performed on a Bellingham and Stanley Ltd. ADP 220 polarimeter. High resolution mass spectrometry was performed by the CAF (Central Analytical Facility) Institute at Stellenbosch University using a Waters API Q-TOF Ultima spectrometer.

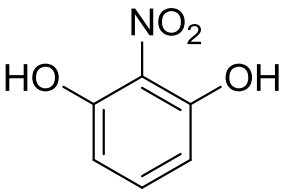
GC-MS was performed on a Carlo Erba QMD 1000 GC–MS system on a capillary column (40 m × 0.3 mm) coated with 0.25 µm apolar PS-089 phase (DB-5 equivalent). The temperature was taken up from 40 °C to 240 °C at 2 °C/min.

Pyridinium *p*-toluenesulfonate (PPTSA)[2] and *trans*-bis(acetonitrile)dichloropalladium(II) $[PdCl_2(MeCN)_2]$ [3] were synthesised according to literature procedures.

7.2 Compounds

7.2.1 Chapter 2

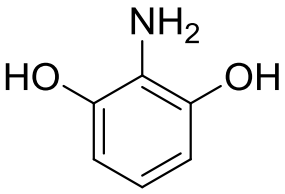
2-Nitrobenzene-1,3-diol (2.1)



2.1 was synthesised according to a modified literature procedure.[4] Concentrated H_2SO_4 (100 ml) was added to resorcinol (22.0 g, 200 mmol) in a 500 ml round-bottom flask and the mixture was left to stir for 30 minutes. The thick, white solution was cooled to 0 °C and a pre-cooled mixture of concentrated HNO_3 (65% v/v, 17.6 ml) and H_2SO_4 (22.4 ml) was added dropwise to the solution over a period of 30 minutes and left to stir for a further 30 minutes after addition. The yellow mixture was carefully diluted with 100 ml of ice-water. The dark orange solution was subjected to steam distillation to furnish an orange crystalline mixture. The mixture was filtered and washed with ice-cold water. The crystalline material was collected and recrystallized from an ethanol-water mixture to yield **2.1** as fine orange needles (7.55 g, 24%).

Mp 79–83 °C (Ethanol/Water) (Lit.[4] m.p. 84 °C); R_f = 0.67 (Petroleum ether/Ethyl acetate, 1:1); IR (ATR): 3241, 3090, 3066, 1623, 1573, 1539, 1438, 1368, 1123, 806 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.62 (d, *J* = 8.4 Hz, 2H, Ar–*H*), 7.44 (t, *J* = 8.4 Hz, 1H, Ar–*H*), 10.66 (s, 2H, –O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 109.6 (Ar–*C*), 139.1 (Ar–*C*), 122.6 (Ar–*C*), 156.4 (Ar–*C*); HRMS–ESI–: *m/z* $[M–H]^-$ calcd for $C_6H_4NO_4$: 154.0140; found: 154.0132.

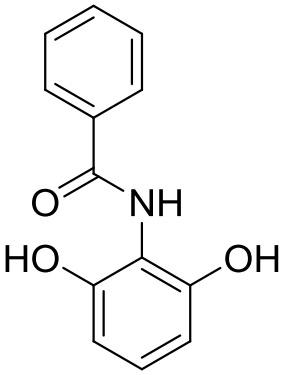
2-Amino-1.3-diol (2.2)



To a mixture of nitroresorcinol **2.1** (3.13 g, 20.2 mmol) in methanol (58 ml) was added Pd/C (10%, 0.535 g, 0.500 mmol). The flask was evacuated and refilled with hydrogen from a balloon. The mixture was stirred at room temperature until completion as monitored by thin layer chromatography (4-5 hours). The mixture was filtered through a Celite plug and washed with methanol and ethyl acetate. The solvent was removed under reduced pressure to leave a brown solid. The solid was purified by flash column chromatography (silica gel eluting with ethyl acetate: hexanes 1:1→ethyl acetate). Finally, the product was triturated with hexane from a warm solution in ethyl acetate to yield a fine yellow-brown powder after drying (2.22 g, 88%). Characterisation data corresponded with literature values.[5-8]

Mp 160–162 °C (Hexane/Ethyl acetate) (Lit.[5] m.p. 152.5 °C); R_f = 0.23 (Hexane/Ethyl acetate, 1:1); IR (ATR): 3363, 3274, 3213, 1602, 1466, 1344, 1157, 949, 768 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 3.82 (br s, 2H, –N*H*), 6.21–6.28 (m, 3H, Ar–*H*), 8.82 (br s, 2H, –O*H*); ^{13}C NMR (DMSO–D_6, 100 MHz, 25 °C): δ = 106.6 (Ar–*C*), 115.8 (Ar–*C*), 123.8 (Ar–*C*), 144.9 (Ar–*C*); HRMS–ESI–: *m/z* $[M–H]^-$ calcd for $C_6H_6NO_2$: 124.0399; found: 124.0390.

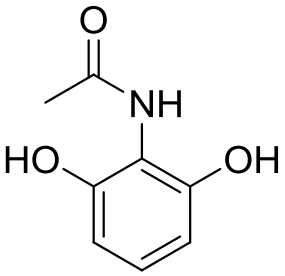
_N_-(2.6-dihydroxyphenyl)benzamide (2.3)



2.3 was synthesised from an adapted literature procedure.[9] A solution of amine **2.2** (500 mg, 4.00 mmol) in tetrahydrofuran (20 ml), in a 2-neck round-bottom flask, was cooled to 0 °C. To the solution was added triethylamine (2.80 ml, 20.0 mmol) and the reaction mixture was stirred for 15 minutes. To this solution was slowly added benzoyl chloride (0.480 ml, 4.12 mmol), after which the mixture was stirred for another 10 minutes at 0 °C. The reaction mixture was warmed to room temperature and left to stir overnight. 5 M KOH (5 ml) was added to the mixture and this was stirred for another two hours. The reaction mixture was acidified to pH 2 with 1 M HCl, carried over to a separatory funnel containing ethyl acetate (60 ml) and the organic phase separated. The water layer was extracted with ethyl acetate (3×60 ml), the organic phases combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a dark brown solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 3:17 → 1:1), to yield a fine brown solid (743 mg, 81%). This material is sufficiently pure to proceed with the next reaction. Further purification can be performed as with the amine **2.2**. Characterisation data corresponded with literature values.[10]

Mp 182–184 °C (Ethyl acetate/Hexane) [Lit.[10] m.p. 187-188 °C (aq. ethanol)]; R_f = 0.44 (Ethyl acetate/Hexane, 1:1); IR (ATR): 3356, 2924, 2848, 1632, 1579, 1537, 1043, 698 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 6.40 (d, *J* = 8.1 Hz, 2H, Ar–*H*), 6.92 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 7.61–7.47 (m, 3H, Ar–*H*), 8.02 (d, *J* = 7.4 Hz, 2H, Ar–*H*), 9.27 (s, 2H, –O*H*), 9.39 (s, 1H, –N*H*); ^{13}C NMR (DMSO–D_6, 100 MHz, 25 °C): δ = 107.1 (Ar–*C*), 113.4 (Ar–*C*), 127.2 (Ar–*C*), 127.9 (Ar–*C*), 128.2 (Ar–*C*), 131.4 (Ar–*C*), 134.2 (Ar–*C*), 153.8 (Ar–*C*), 165.8 (C=O); HRMS–ESI–: *m/z* $[M–H]^-$ calcd for $C_{13}H_{10}NO_3$: 228.0661; found: 228.0648.

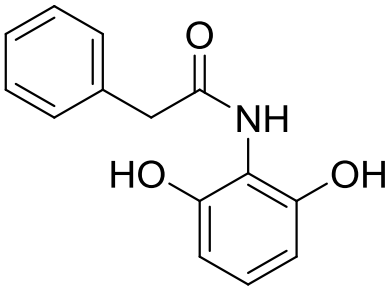
_N_-(2,6-dihydroxyphenyl)acetamide (2.4)



This molecule was synthesised using an analogous method as for the benzamide **2.3**: Amine (500 mg, 4.00 mmol), acetylchloride (0.300 ml, 4.12 mmol) and triethylamine (2.80 ml, 20.0 mmol) in tetrahydrofuran (20 ml) was used. The dark brown solid product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:4→1:1), yielding a light-brown solid (602 mg, 90%). Further purification can be performed in the same manner as the amine **2.2**. Characterisation data corresponded with available literature values, except the melting point, though this was likely due to a different polymorph owing to the different crystallisation solvent used.[11]

Mp 178–180 °C (dec) (Hexane/Ethyl acetate) [Lit.[11] m.p. 95.5-97.1 °C (ethanol)]; R_f = 0.23 (Hexane/Ethyl acetate, 1:1); IR (ATR): 3379, 3250, 1653, 1585, 1535, 1464, 1338, 1024, 642 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 2.11 (s, 3H, –C*H*$_3$), 6.35 (d, *J* = 8.2 Hz, 2H, Ar–*H*), 6.87 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 9.33 (br s, 3H, –O*H*, –N*H*); ^{13}C NMR (DMSO–D_6, 100 MHz, 25 °C): δ = 22.7 (–*C*H$_3$), 107.5 (Ar–*C*), 114.0 (Ar–*C*), 126.5 (Ar–*C*), 151.9 (Ar–*C*), 170.2 (C=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_8H_{10}NO_3$: 168.0661; found: 168.0676.

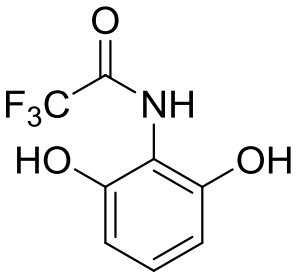
_N_-(2,6-dihydroxyphenyl)-2-phenylacetamide (2.5)



To a solution of 2-phenylacetic acid (572 mg, 4.20 mmol) in dichloromethane (10 ml) at 0 °C, was slowly added thionyl chloride (3.0 ml, 42 mmol). The solution was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo* to leave the crude acyl chloride, which was kept under vacuum for another 20 minutes to remove all traces of thionyl chloride. To a mixture of amine **2.2** (500 mg, 4.00 mmol) in tetrahydrofuran (20 ml) at 0 °C was added triethylamine (3.35 ml, 24.0 mmol) and the reaction stirred for 15 minutes. To this solution was slowly added the acyl chloride dissolved in dichloromethane (6 ml). The reaction was stirred for 10 minutes at 0 °C and then slowly warmed to room temperature and left to stir overnight. Work-up of the reaction is the same as for **3**. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 3:17 → 1:1), to yield a white solid (613 mg, 63%). Further purification can be performed in the same manner as the amine **2.2**.

Mp 164–165 °C (Ethyl acetate/Hexane); R_f = 0.48 (Ethyl acetate/Hexane, 1:1); IR (ATR): 3357, 3174, 2945, 1632, 1586, 1541, 1476, 1181, 1040, 750 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 3.78 (s, 2H, –C*H*$_2$–Ph), 6.37 (d, *J* = 8.1 Hz, 2H, Ar–*H*), 6.88 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 7.21–7.43 (m, 5H, Ar–*H* (Ph)), 9.38 (s, 2H, –O*H*), 9.54 (s, 1H, –N*H*); ^{13}C NMR (DMSO–D_6, 100 MHz, 25 °C): δ = 41.9 (–*C*H$_2$–Ph), 107.6 (Ar–*C*), 113.9 (Ar–*C*), 126.5 (Ar–*C*), 126.8 (Ar–*C*), 128.3 (Ar–*C*), 129.2 (Ar–*C*), 136.1 (Ar–*C*), 152.1 (Ar–*C*), 171.0 (C=O); HRMS–ESI–: *m/z* $[M–H]^-$ calcd for $C_{14}H_{12}NO_3$: 242.0817; found: 242.0810.

_N_-(2,6-dihydroxyphenyl)-2,2,2-trifluoroacetamide (2.6)

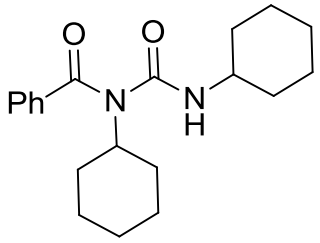


2.6 was synthesised from an adapted literature procedure.[12] To a solution of amine **2.2** (700 mg, 5.60 mmol) in tetrahydrofuran (28 ml) at 0 °C was added pyridine (0.900 ml, 11.2 mmol). The reaction was stirred for 15 minutes, after which trifluoroacetic anhydride (1.03 ml, 7.30 mmol) was slowly added to the solution. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. After 18 hours the reaction was quenched with half saturated brine (20 ml, 1:1 v/v). The reaction mixture was carried over to a separatory funnel containing more half saturated brine (50 ml, 1:1 v/v). The mixture was extracted with ethyl acetate (3×70 ml), the organic phases combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave an orange oil that slowly solidifies on standing. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:4 → 3:7→ 1:1), to yield a yellow solid (1.21 g, 97%) after drying on a high vacuum pump. This material is sufficiently pure to proceed with the next reaction.

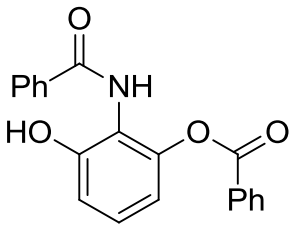
Mp 156–158 °C (Ethyl acetate/Hexane); R_f = 0.52 (Ethyl acetate/Hexane, 1:1); IR (ATR): 3350, 3091, 1711, 1612, 1541, 1473, 1155, 1024, 750 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 6.36 (d, *J* = 8.2 Hz, 2H, Ar–*H*), 6.94 (t, *J* = 8.2 Hz, 1H, Ar–*H*), 9.52 (s, 2H, –O*H*), 10.15 (br s, 1H, –N*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 106.5 (Ar–*C*), 109.7 (Ar–*C*), 116.2 (q, $J_{C\text{-}F}$ = 288.8 Hz, –*C*F$_3$), 128.2 (Ar–*C*), 154.4 (Ar–*C*), 155.3 (q, $J_{C\text{-}F}$ = 35.6 Hz *C*=O); ^{19}F NMR (DMSO–D_6, 282 MHz, 25 °C): δ = –73 (–C*F*$_3$); HRMS–ESI–: *m/z* $[M–H]^-$ calcd for $C_8H_5NO_3F_3$: 220.0222; found: 220.0212.

_N_-Cyclohexyl-_N_-(cyclohexylcarbamoyl)benzamide (2.7) and 2-Benzamido-3-hydroxyphenyl benzoate (2.8)

To a suspension of benzoic acid (147 mg, 1.20 mmol) and amine **2.2** (150 mg, 1.20mmol) in dry dichloromethane (8 ml) at 0 °C was added dicyclohexylcarbodiimide (248 mg, 1.20 mmol). The mixture was stirred for a further 15 minutes at 0 °C, after which it was warmed to room temperature and left to stir overnight. The reaction mixture was filtered through a plug of Celite and washed with dichloromethane (10 ml). The solution was consecutively washed with 1M HCl (5 ml), H_2O (5 ml) and brine (5 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to yield a brown solid. The product was purified by using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:4→1:1) to yield product **2.7**[13] (126 mg, 32%) and **2.8** (96.1 mg, 48%) respectively. The compounds were only partially characterised.



2.7



2.8

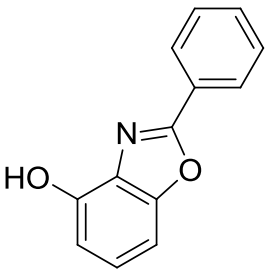
2.7: R_f = 0.70 (Ethyl acetate/Hexane, 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.76–0.92 (m, 2H, Cyclopentyl), 0.97–1.30 (m, 6H, Cyclopentyl), 1.42–1.63 (m, 6H, Cyclopentyl), 1.72–1.86 (m, 4H, Cyclopentyl), 1.92–2.11 (m, 2H, Cyclopentyl), 3.37–3.53 (m, 1H, –C*H*), 4.08 (tt, *J* = 12.0, 3.6 Hz, 1H, –C*H*), 6.16 (d, *J* = 8.0 Hz, 1H, –N*H*), 7.32–7.48 (m, 3H, Ar–*H*), 7.48–7.57 (m, 2H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 24.6 (Cyclopentyl), 25.4 (Cyclopentyl), 25.5 (Cyclopentyl), 26.3 (Cyclopentyl), 30.8 (Cyclopentyl), 32.3 (Cyclopentyl), 49.7 (–*C*H), 57.5 (–*C*H), 126.8 (Ar–*C*), 128.6 (Ar–*C*), 130.8 (Ar–*C*), 137.1 (Ar–*C*), 154.4 (–*C*(O)–NH), 171.4 (C–*C*(O)–N).

2.8: R_f = 0.47 (Ethyl acetate/hexane, 1:1); ^{1}H NMR (DMSO–D_6, 400 MHz, 50 °C): δ = 6.86 (dd, *J* = 8.3, 1.3 Hz, 1H, Ar–*H*), 6.89 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar–*H*), 7.21 (t, *J* = 8.2 Hz, 1H, Ar–*H*), 7.36–7.43 (m, 2H, Ar–*H*), 7.44–7.51 (m, 3H, Ar–*H*), 7.60–7.66 (m, 1H, Ar–*H*), 7.81–7.87 (m, 2H, Ar–*H*), 7.97–8.04 (m, 2H, Ar–*H*), 9.56 (br s, 2H, N*H* and O*H*); ^{13}C NMR (DMSO–D_6, 100 MHz, 50 °C): δ = 113.2 (Ar–*C*), 113.5 (Ar–*C*), 118.1 (Ar–*C*), 126.8 (Ar–*C*), 127.4 (Ar–*C*), 127.9 (Ar–*C*), 128.5 (Ar–*C*), 129.1 (Ar–*C*), 129.3 (Ar–*C*), 131.0 (Ar–*C*), 133.5 (Ar–*C*), 134.2 (Ar–*C*), 147.6 (Ar–*C*), 154.2 (Ar–*C*), 163.5 (*C*=O), 165.6 (*C*=O).

Cyclodehydration reactions

The following synthesis of benzoxazole **2.9** is a representative method for the synthesis of benzoxazoles **2.9-2.12**:

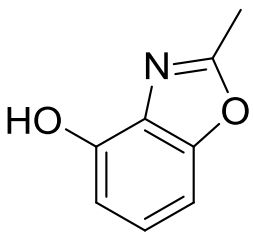
2-Phenyl-1,3-benzoxazol-4-ol (2.9)



Phenylamide **2.3** (412 mg, 1.80 mmol), pyridinium *p*-toluenesulfonate (23 mg, 0.090 mmol) in toluene (20 ml) was warmed to reflux and followed to completion by thin layer chromatography (six days). The mixture was allowed to cool to room temperature and added to H_2O (50 ml) and the mixture was extracted with ethyl acetate (3×50 ml). The organic phases were combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to yield a yellow solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 3:7→ 1:1), to yield an off-white solid. The solid was recrystallised from a mixture of toluene/hexane to yield white fibre-like crystals (310 mg, 82%). Characterisation data corresponded with literature values.[14]

Mp 131–133 °C (Toluene/Hexane) [Lit.[14] m.p. 138-139 °C (benzene)]; R_f = 0.56 (Hexane/Ethyl acetate, 1:1); IR (ATR): 3462, 3008, 2646, 1614, 1552, 1456, 1275, 1053, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 6.92 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar–*H*), 7.15 (dd, *J* = 8.2, 0.9 Hz, 1H, Ar–*H*), 7.26 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 7.44–7.56 (m, 3H, Ar–*H*(Ph)), 8.14–8.24 (m, 2H, Ar–*H*(Ph)), 8.40 (s, 1H, –O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 102.7 (Ar–*C*), 111.2 (Ar–*C*), 126.4 (Ar–*C*), 126.9 (Ar–*C*), 127.7 (Ar–*C*), 129.1 (Ar–*C*), 130.6 (Ar–*C*), 131.7 (Ar–*C*), 148.3 (Ar–*C*), 152.0 (Ar–*C*), 161.9 (N=*C*–O); HRMS–ESI–: *m/z* $[M–H]^-$ calcd for $C_{13}H_8NO_2$: 210.0555; found: 210.0549.

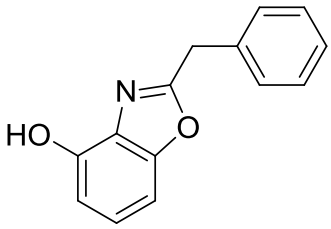
2-Methyl-1,3-benzoxazol-4-ol (2.10)



Synthesised in an analogous method to **2.9**. Methylamide **2.4** (650 mg, 3.89 mmol) and pyridinium *p*-toluenesulfonate (98 mg, 0.39 mmol) in toluene (40 ml). The product was purified by using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:4→ 1:1) and recrystallised from a mixture of ethyl acetate/hexane to yield fine colourless crystals (516 mg, 89%). Characterisation data corresponded with literature values.[15]

Mp 144–146 °C (Ethyl acetate/Hexane) [Lit.[15] m.p. 139-140 °C (dichloromethane/hexane)]; R_f = 0.50 (Hexane/Ethyl acetate, 1:1); IR (ATR): 3082, 1627, 1608, 1572, 1499, 1233, 1183, 1056, 952, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 2.71 (s, 3H, –C*H*$_3$), 6.89 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar–*H*), 7.04 (dd, *J* = 8.2, 0.9 Hz, 1H, Ar–*H*), 7.22 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 10.28 (s, 1H, –O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 14.3 (–*C*H_3), 101.9 (Ar–*C*), 111.3 (Ar–*C*), 126.0 (Ar–*C*), 129.1 (Ar–*C*), 148.3 (Ar–*C*), 152.2 (Ar–*C*), 163.7 (N=*C*–O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_8H_8NO_2$: 150.0555; found: 150.0552.

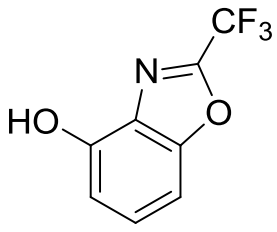
2-Benzyl-1,3-benzoxazol-4-ol (2.11)



Synthesised in an analogous method to **2.9**: Benzylamide **2.5** (410 mg, 1.69 mmol) and pyridinium *p*-toluenesulfonate (22 mg, 0.090 mmol) in toluene (17 ml) was used. Resulting yellowish solid was purified by using flash column chromatography (silica gel eluting with ethyl acetate: hexane 3:7→ 1:3→ 1:1) and recrystallised from of ethyl acetate to yield fine light-yellow crystals (325 mg, 85%). Characterisation data corresponded with literature values.[16]

Mp 185–186 °C (Ethyl acetate) [Lit.[16] m.p. 189 °C (aq. ethanol)]; R_f = 0.54 (Ethyl acetate/Hexane, 1:1); IR (ATR): 3095, 3026, 1632, 1608, 1560, 1493, 1448, 1240, 1039, 706 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 4.29 (s, 2H, –C*H*$_2$–Ph), 6.70 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar–*H*), 7.04 (dd, *J* = 8.2, 0.9 Hz, 1H, Ar–*H*), 7.12 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 7.25–7.39 (m, 5H, Ar–*H*(Ph)), 10.20 (s, 1H, –O*H*); ^{13}C NMR (DMSO–D_6, 100 MHz, 25 °C): δ = 34.1 (–*C*H_2–Ph), 101.1 (Ar–*C*), 110.1 (Ar–*C*), 125.3 (Ar–*C*), 127.0 (Ar–*C*), 128.6 (Ar–*C*), 129.0 (Ar–*C*), 129.5 (Ar–*C*), 135.4 (Ar–*C*), 149.1 (Ar–*C*), 152.1 (Ar–*C*), 163.0 (N=*C*–O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}NO_2$: 226.0868; found: 226.0867.

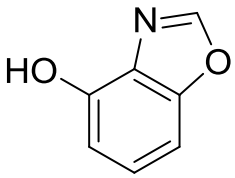
2-Trifluoromethyl-1,3-benzoxazol-4-ol (2.12)



Synthesised in an analogous method to **2.9**: Trifluoroacetamide **2.6** (1.19 g, 5.36 mmol) and pyridinium *p*-toluenesulfonate (202 mg, 0.800 mmol) in toluene (54 ml) was used. The solvent was removed and the colourless oil was subjected to flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:4→1:0). The resulting colourless oil was dissolved in the minimum amount of hexane and placed in a fridge at −20 °C. Small white crystals formed after a few days. The crystals was collected by filtration and washed with cold hexane (−20 °C) to yield **2.12** as fine off-white crystals (892 mg, 82%).

Mp 40–42 °C (Hexane); R_f = 0.62 (Ethyl acetate/Hexane, 1:1); IR (ATR): 3269, 3057, 1622, 1583, 1504, 1446, 1369, 1113, 1039, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 6.98 (dd, *J* = 8.2, 0.8 Hz, 1H, Ar–*H*), 7.19 (dd, *J* = 8.4, 0.8 Hz, 1H, Ar–*H*), 7.41 (t, *J* = 8.3 Hz, 1H, Ar–*H*), 7.72 (br s, 1H, –O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 103.4 (Ar–*C*), 112.0 (Ar–*C*), 116.8 (q, J_{C-F} = 271.6 Hz, –*C*F_3), 128.2 (Ar–*C*), 129.3 (Ar–*C*), 149.3 (Ar–*C*), 150.4 (q, J_{C-F} = 44.0 Hz, N=*C*(CF_3)–O), 151.9 (Ar–*C*); ^{19}F NMR ($CDCl_3$, 376 MHz, 25 °C): δ = –66 (–*C*F_3); HRMS–ESI–: *m/z* $[M–H]^-$ calcd for $C_8H_3NO_2F_3$: 202.0116; found: 202.0114;

1,3-Benzoxazol-4-ol (2.13)



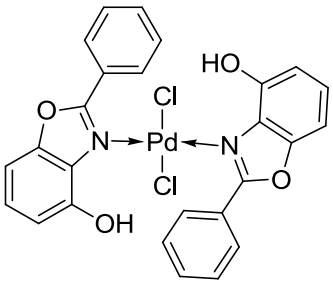
Amine **2.2** (858 mg, 6.86 mmol) and pyridinium *p*-toluenesulfonate (259 mg, 1.03 mmol) was suspended in toluene (69 ml). To this mixture was added trimethyl orthoformate (1.50 ml, 13.7 mmol) and warmed to reflux. The reaction was monitored by thin layer chromatography till completion (2 hours). The solvent was removed under reduced pressure and taken up in ethyl acetate (200 ml) and washed with 1M HCl, water and brine (50 ml each). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave an orange solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:3 → 1:1), to yield a yellow solid (824 mg, 89%). This material is sufficiently pure to proceed with the next reactions. Characterisation data corresponded with literature values.[16]

Mp 186–190 °C (Ethyl acetate/Hexane) [Lit.[16] m.p. 190 °C (aq. ethanol)]; R_f = 0.54 (Hexane/Ethyl acetate, 2:3); IR (ATR): 3113, 1614, 1600, 1500, 1309, 1244, 1032, 706 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 6.77 (dd, *J* = 7.9, 1.0 Hz, 1H, Ar–*H*), 7.14 (dd, *J* = 8.2, 1.0 Hz, 1H, Ar–*H*), 7.20 (t, *J* = 8.0 Hz, 1H, Ar–*H*), 8.55 (s, 1H, =C–*H*), 10.33 (s, 1H, –O*H*); ^{13}C NMR (DMSO–D_6, 100 MHz, 25 °C): δ = 101.6 (Ar–*C*), 110.2 (Ar–*C*), 126.1 (Ar–*C*), 128.6 (Ar–*C*), 149.8 (Ar–*C*), 151.2 (Ar–*C*), 152.1 (N=*C*–O); HRMS–ESI–: *m/z* $[M–H]^-$ calcd for $C_7H_4NO_2$: 134.0242; found: 134.0235.

7.2.2 Chapter 3

Due to the inherently low solubility of these compounds they could not all be fully characterised (refer to Chapter 3 for more information). Details of the crystal structures of some of the compounds can be found in Section 7.3 and should be used in conjunction with the information given in the text below.

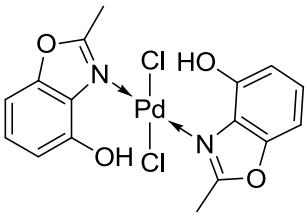
Bis(2-Phenyl-1,3-benzoxazol-4-ol-κ^1*N*)dichloropalladium(II) (2.9a)



Benzoxazole **2.9** (85 mg, 0.40 mmol) and dichloromethane (3 ml) was added to a Schlenk flask and the mixture stirred until completely dissolved. To this was added [$PdCl_2(MeCN)_2$] (52 mg, 0.20 mmol) and more dichloromethane (2 ml). The reaction was stirred at room temperature for eight hours, during which time the reaction went from yellow to orange and a fine yellow precipitate was formed very slowly. The reaction was filtered and washed with cold dichloromethane (0 °C) and a yellow powder was recovered. The solvent of the filtrate was removed under reduced pressure to leave a yellow solid, which was taken up in the least amount of warm dichloromethane and placed in a freezer at −20 °C. Small light-orange crystals formed after a few days. The crystals were collected by filtration and washed with cold dichloromethane and hexane (−20 °C) to yield light-orange crystals. IR spectroscopy revealed the powder and crystals to be the same product, giving a combined yield of **2.9a** (66 mg, 55%).

Mp >250 °C (dec) (dichloromethane); IR (ATR): 3243, 1631, 1591, 1358, 1285, 1038, 775, 734 cm^{-1}; ^{1}H NMR (DMSO–D_6/$CDCl_3$, 400 MHz, 25 °C): δ = 6.97–7.15 (m, 4H, Ar–*H*), 7.23–7.36 (m, 2H, Ar–*H*), 7.38–7.47 (m, 3H, Ar–*H*), 7.60–7.77 (m, 4H, Ar–*H*), 8.85–8.94 (m, 2H, Ar–*H*), 9.49–9.61 (m, 1H, Ar–*H*), 10.53 (br s, 1H, O*H*), 10.80 (br s, 1H, O*H*).

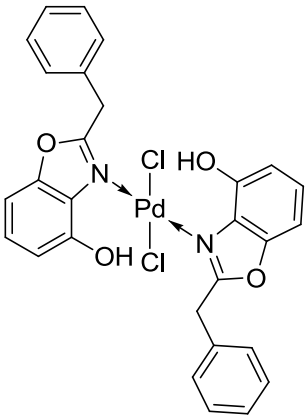
Bis(2-Methyl-1,3-benzoxazol-4-ol-κ^1*N*)dichloropalladium(II) (2.10a)



Benzoxazole **2.10** (45 mg, 0.30 mmol) was dissolved in dichloromethane (2 ml). To this was added [$PdCl_2(MeCN)_2$] (39 mg, 0.15 mmol) and more dichloromethane (2 ml) to form a clear yellow solution. Within five minutes a precipitate forms and the reaction was left to stir at room temperature for three hours. The light yellow precipitate was collected by filtration and washed with cold dichloromethane and hexane (0 °C) to yield **2.10a** (36 mg, 74%) after drying under high vacuum.

Mp >250 °C (dec); IR (ATR): 3243, 1631, 1591, 1505, 1453, 1285, 1190, 1038, 987, 775 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 2.94–3.15 (m, 6H, –C*H*$_3$), 6.84–6.97 (m, 2H, Ar–*H*), 7.16–7.25 (m, 2H, Ar–*H*), 7.27–7.36 (m, 2H, Ar–*H*).

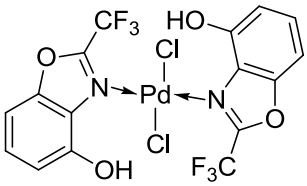
Bis(2-Benzyl-1,3-benzoxazol-4-ol-κ^1*N*)dichloropalladium(II) (2.11a)



Benzoxazole **2.11** (90 mg, 0.40 mmol) and tetrahydrofuran (10 ml) was added to a Schlenk flask and the mixture stirred until completely dissolved. To this was added [$PdCl_2(MeCN)_2$] (52 mg, 0.20 mmol) in dichloromethane (4 ml) to form a light yellow solution. Almost immediately precipitation starting forming and the reaction was left to stir for three hours at room temperature. The light yellow precipitate was collected by filtration and washed with cold hexane (0 °C) to yield **2.11a** (108 mg, 86%) after drying under high vacuum.

Mp >250 °C (dec); IR (ATR): 3114, 2988, 1630, 1577, 1364, 1285, 1041, 886, 750 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 4.29 (br s, 4H, –C*H*$_2$), 6.92–7.00 (m, 2H, Ar–*H*), 7.13–7.21 (m, 2H, Ar–*H*), 7.25–7.47 (m, 9H, Ar–*H*), 7.72–7.84 (m, 3H, Ar–*H*), 11.34 (br s, 2H, O*H*).

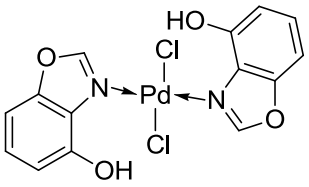
Bis(2-Trifluoromethyl-1,3-benzoxazol-4-ol-κ^1*N*)dichloropalladium(II) (2.12a)



Benzoxazole **2.12** (81 mg, 0.40 mmol) and dichloromethane (5 ml) was added to a Schlenk flask and the mixture stirred until completely dissolved. To this was added [$PdCl_2(MeCN)_2$] (52 mg, 0.20 mmol) in dichloromethane (3 ml) to form a light yellow solution. A precipitation was slowly starting to form after 25 minutes and the reaction was left to stir overnight at room temperature. The light yellow precipitate was collected by filtration and washed with cold dichloromethane and hexane (0 °C) to yield **2.12a** (74 mg, 64%) after drying under high vacuum.

Mp 230 °C (dec); IR (ATR): 3447, 3278, 1635, 1609, 1582, 1394, 1224, 1145, 775 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 6.91 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar–*H*), 7.31 (dd, *J* = 8.3, 0.9 Hz, 1H, Ar–*H*), 7.43 (t, *J* = 8.2 Hz, 1H, Ar–*H*), 10.88 (br s, 1H, O*H*).

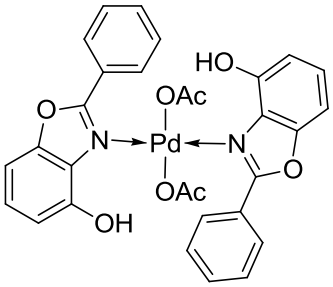
Bis(1,3-Benzoxazol-4-ol-κ^1*N*)dichloropalladium(II) (2.13a)



Benzoxazole **2.13** (54 mg, 0.40 mmol) and tetrahydrofuran (10 ml) was added to a Schlenk flask and the mixture stirred until completely dissolved. To this was added [$PdCl_2(MeCN)_2$] (52 mg, 0.20 mmol) in dichloromethane (4 ml) to form a light yellow solution. Precipitation starting forming very slowly and the reaction was left to stir overnight at room temperature. The light yellow precipitate was collected by filtration and washed with cold hexane (0 °C) to yield **2.13a** (45 mg, 50%) after drying under high vacuum.

Mp >250 °C (dec); IR (ATR): 3284, 3103, 3053, 1630, 1620, 1508, 1304, 1024, 997, 731 cm^{-1}; ^{1}H NMR (DMSO–D_6, 400MHz, 25°C): δ = 6.74 (d, *J* = 7.7 Hz, 1H, Ar–*H*), 7.12 (d, *J* = 7.7 Hz, 1H, Ar–*H*), 7.19 (t, *J* = 7.6 Hz, 1H, Ar–*H*), 8.53 (s, 1H, *H*–C=N), 10.30 (s, 1H, O*H*).

Bis(2-Phenyl-1,3-benzoxazol-4-ol-κ^1*N*)diacetatopalladium(II) (2.9b)



Benzoxazole **2.9** (85 mg, 0.40 mmol) and dichloromethane (5 ml) was added to a Schlenk flask and the mixture stirred until completely dissolved. To this was added $Pd(OAc)_2$ (45 mg, 0.20 mmol) and more dichloromethane (1 ml). The reaction was stirred overnight at room temperature, during which time a fine precipitate formed. The reaction was filtered and washed with cold dichloromethane (0 °C) and a yellow powder was recovered. The solvent of the filtrate was removed under reduced pressure to leave a yellow solid, which was taken up in the least amount of warm dichloromethane and placed in a freezer at −20 °C. Small light-yellow crystals formed after a few days. The crystals was collected by filtration and washed with cold dichloromethane and hexane (−20 °C) to yield light-yellow crystals. IR spectroscopy revealed the powder and crystals to be the same product, giving a combined yield of **2.9b** (46 mg, 35%)

Mp 180–185 °C (dec); IR (ATR): 2940, 2820, 2629, 1635, 1598, 1570, 1334, 1272, 736, 680 cm^{-1}; ^{1}H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 1.77 (br s, 3H, –CH_3), 1.91 (br s, 3H, –CH_3), 6.79 (dd, *J* = 7.2, 1.7 Hz, 2H, Ar–*H*), 7.14–7.27 (m, 4H, Ar–*H*), 7.51–7.71 (m, 6H, Ar–*H*), 8.08–8.25 (m, 4H, Ar–*H*).

Reaction of $Pd(OAc)_2$ with 2-Methyl-1,3-benzoxazol-4-ol (2.10b)

Benzoxazole **2.10** (75 mg, 0.50 mmol) was dissolved in dichloromethane (3 ml). To this was added $Pd(OAc)_2$ (56 mg, 0.25 mmol) and more dichloromethane (2 ml) to form a clear orange solution. Within five minutes a precipitate formed and the reaction was left to stir overnight at room temperature. The light yellow precipitate was collected by filtration and washed with cold dichloromethane and hexane (0 °C) to yield **2.10b** (87 mg) after drying under high vacuum.

Mp 200 °C (dec); IR (ATR): 3107, 2936, 2635, 1633, 1602, 1561, 1370, 1331, 1266, 708 cm^{-1}.

Reaction of $Pd(OAc)_2$ with 2-Benzyl-1,3-benzoxazol-4-ol (2.11b)

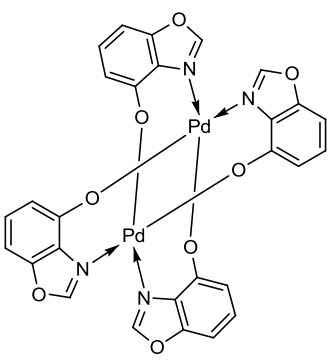
Benzoxazole **2.11** (45 mg, 0.20 mmol) and tetrahydrofuran (5 ml) was added to a Schlenk flask and the mixture stirred until completely dissolved. To this was added $Pd(OAc)_2$ (23 mg, 0.10 mmol) in dichloromethane (2 ml) to form an orange solution and the reaction was left to stir for a day at room temperature. The solvent of the reaction was removed and the orange solid was taken up in dichloromethane. The solution was treated with hexane and an orange solid precipitated out. The orange precipitate was collected by filtration and washed with cold hexane (0 °C) to yield **2.11b** (35 mg, mixture of compounds) after drying under high vacuum.

Mp 152–160 °C (dec); IR (ATR): 3029, 2640, 1615, 1602, 1569, 1270, 1047, 737 cm^{-1}.

Reaction of $Pd(OAc)_2$ with 2-Trifluoromethyl-1,3-benzoxazol-4-ol (2.12b)

Benzoxazole **2.12** (102 mg, 0.500 mmol) was dissolved in dichloromethane (3 ml). To this was added $Pd(OAc)_2$ (56 mg, 0.25 mmol) and more dichloromethane (2 ml) to form a clear orange solution. The reaction was left to stir overnight at room temperature, turning dark-brown. Work-up revealed the formation of Pd(0) and decomposed ligand.

Reaction of $Pd(OAc)_2$ with 1,3-Benzoxazol-4-ol to form tetrakis(μ_2-1,3-Benzoxazol-4-olate)-dipalladium(II) (2.13b)



Benzoxazole **2.13** (54 mg, 0.40 mmol) and tetrahydrofuran (10 ml) was added to a Schlenk flask and the mixture stirred until completely dissolved. To this was added $Pd(OAc)_2$ (45 mg, 0.20 mmol) in dichloromethane (4 ml) to form a light yellow solution. Precipitation starting forming on addition of the metal

salt and the reaction was left to stir overnight at room temperature. The orange precipitate was collected by filtration and washed with cold dichloromethane and hexane (0 °C) to yield **2.13b** (60 mg, 40%) after drying under high vacuum.

Mp 190 °C (dec); IR (ATR): 3060, 3010, 2979, 1615, 1567, 1471, 1285, 1141, 1043, 720 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 6.55–6.65 (m, 4H, Ar–*H*), 6.72 (d, *J* = 7.8 Hz, 4H, Ar–*H*), 6.88–6.97 (m, 4H, Ar–*H*), 9.29 and 9.59 (br s, 4H, *H*–C=N).

General procedure for the Heck coupling of styrene with bromobenzene

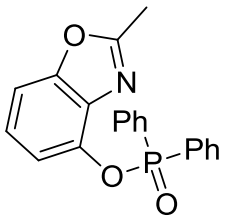
To a solution of **2.10a** in dimethylformamide (5 ml) was added base (4.0 mmol), bromobenzene (0.21 ml, 2.0 mmol) and styrene (0.29 ml, 2.5 mmol). The reaction vessel was placed in an oil bath and the reaction warmed to reflux and left for the indicated time. The reaction mixture was cooled to room temperature, filtered through Celite and washed with dichloromethane (30 ml). The mixture was taken up in a separatory funnel and washed with 1 M HCl (2x25 ml), H_2O (25 ml) and finally with brine (25 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a brown solid. The product was purified using flash column chromatography (silica gel eluting with hexane followed by ethyl acetate: hexane 1:9), to yield a white solid and compared with the ^1H NMR spectrum of the compound in literature.

General procedure for the Heck coupling of styrene with iodobenzene

To a solution of the metal complex **2.9a-2.13a** (1mol%) in dimethylformamide (5 ml) was added triethylamine (0.14 ml, 1.0 mmol), iodobenzene (0.11 ml, 1.0 mmol) and styrene (0.17 ml, 1.5 mmol). The reaction vessel was placed in an oil bath at 100 °C and warmed to 120 °C and left for the indicated time (23 hours). The reaction mixture was cooled to room temperature, and a sample was taken (0.50 ml). The sample was filtered through 45 µm syringe filters, diluted with dichloromethane to 10 ml and a pre-weighted amount of *p*-xylene added as internal standard. 1.0 µl of the sample was injected into a GC-MS and the conversion of iodobenzene and the formation of the products calculated based on the internal standard and the response factor of pure stilbene.

7.2.3 Chapter 4

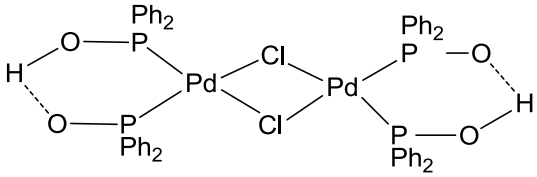
2-Methyl-1,3-benzoxazol-4-yl diphenylphosphinate (4.1)



Methylbenzoxazole **2.10** (75 mg, 0.50 mmol), DMAP (6 mg, 0.05 mmol) and triethylamine (0.15 ml, 1.1 mmol) was dissolved in de-gassed tetrahydrofuran (5 ml) and cooled to 0 °C. To this mixture diphenylphosphine chloride (0.10 ml, 0.55 mmol) was added dropwise. The mixture formed an instant white precipitate. The mixture was slowly warmed to room temperature and left stirring for a further four hours. The reaction was filtered over Celite and the solvent removed under reduced pressure. The resulting yellowish solid was purified by flash column chromatography over a short plug of alumina (eluting with ethyl acetate: hexane 3:7→1:1) to yield a whitish gummy solid that solidified over time (105 mg, 60%).

R_f = 0.30 (Ethyl acetate\Petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 2.64 (s, 3H, –C*H*$_3$), 7.11 (t, *J* = 8.2 Hz, 1H, Ar–*H*), 7.20 (dt, *J* = 8.2, 0.8 Hz, 1H, Ar–*H*), 7.36–7.39 (m, 1H, Ar–*H*), 7.41–7.54 (m, 6H, Ar–*H*), 7.96–8.06 (m, 4H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 14.7 (–*C*H$_3$), 106.9 (Ar–*C*), 116.0, 116.1 (Ar–*C*), 124.9 (Ar–*C*), 128.0 (Ar–*C*), 128.4 (Ar–*C*), 128.6, 128.7 (Ar–*C*), 128.7 (Ar–*C*), 130.2 (Ar–*C*), 131.6 (Ar–*C*), 131.8 (Ar–*C*), 131.9 (Ar–*C*), 132.1, 132.2 (Ar–*C*), 132.3, 132.4 (Ar–*C*), 132.6, 132.6 (Ar–*C*), 133.6, 133.7 (Ar–*C*), 141.8, 141.9 (Ar–*C*), 152.7 (Ar–*C*), 163.7 (N–*C*=O); ^{31}P NMR ($CDCl_3$, 161.5 MHz, 25°C): δ = 32.6; HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}NO_3P$: 350.0946; found: 350.0927.

[{Pd(*μ*-Cl)(PPh_2O)(PPh_2OH)}$_2$] (4.2)



The product was isolated as a by-product from the following reaction:

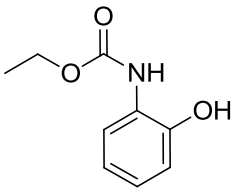
Methylbenzoxazole **2.10** (100 mg, 0.670 mmol), DMAP (9 mg, 0.07 mmol) and triethylamine (0.210 ml, 1.47 ml) was dissolved in de-gassed tetrahydrofuran (7 ml) and cooled to 0 °C. To this mixture diphenylphosphine chloride (0.15 ml, 0.80 mmol) was added dropwise. The mixture forms an instant white precipitation. The mixture was slowly warmed to room temperature and left stirring for a further four hours. To this was added a mixture of $[PdCl_2(MeCN)_2]$ (174 mg, 0.670 mmol) in dichloromethane (8 ml) and the resulting orange solution stirred for four hours. The mixture was filtered through Celite, washed with

dichloromethane and the solvent removed. The resulting orange solid was taken up in a minimum amount of dichloromethane and layered with hexane. A fine yellow solid of **4.2** was recovered. Characterisation data corresponded with literature values.[17]

Mp 193 °C(dec) (dichloromethane/hexane) [Lit.[17] m.p. 187-190 °C (dec)]; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.20–7.30 (m, 18H, Ar–*H*), 7.34–7.43 (m, 8H, Ar–*H*), 7.51–7.61 (m, 14H, Ar–*H*); ^{31}P NMR ($CDCl_3$, 121.5 MHz, 25 °C): δ = 79.0.

7.2.4 Chapter 5

Ethyl 2-hydroxyphenylcarbamate (5.1)

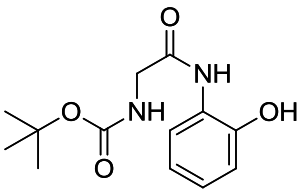


The product was isolated as a by-product from the following reaction and was not fully characterised:

To a solution of *N*-Boc-glycine (175 mg, 1.00 mmol) in tetrahydrofuran (2 ml) at 0 °C was added triethylamine (0.14 ml, 1.0 mmol). Ethyl chloroformate (0.13 ml, 1.0 mmol) was added slowly to the reaction mixture and the solution was stirred for 30 minutes. 2-Aminophenol (131 mg, 1.20 mmol) in tetrahydrofuran (2 ml) was added dropwise to the solution and the resulting mixture was left to stir for one hour at 0 °C. The thick brown mixture was warmed to room temperature and left to stir overnight. 1M HCl (25 ml) was added to the mixture and carried over to a separatory funnel containing ethyl acetate (25 ml) and the organic phase separated. The water layer was extracted with ethyl acetate (2×25 ml), the organic phases combined and dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent removed under reduced pressure to leave a dark brown oil. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 3:17 → 3:7→1:0), to yield **5.1** as a light yellow solid (40 mg, 22 %).

R_f = 0.46 (Heptane/ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.33 (t, *J* = 6.9 Hz, 3H, –C*H*$_3$), 4.26 (q, *J* = 6.9 Hz, 2H, –C*H*$_2$), 6.80–7.09 (m, 4H, Ar–*H*), 7.24 (d, *J* = 8.2 Hz, 1H, Ar–N*H*), 7.72 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 14.6 (–*C*H$_3$), 62.4 (–*C*H$_2$), 118.5 (Ar–*C*), 121.1 (Ar–*C*), 121.4 (Ar–*C*), 125.5 (Ar–*C*), 125.7 (Ar–*C*), 147.2 (Ar–*C*–OH), 155.6 (*C*=O).

***tert*-Butyl (2-((2-hydroxyphenyl)amino)-2-oxoethyl)carbamate (5.2)**

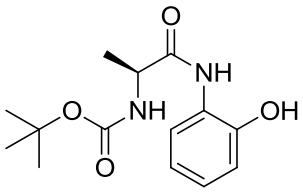


N-Boc-glycine (350 mg, 2.00 mmol) and 2-aminophenol (218 mg, 2.00 mmol) was dissolved in acetonitrile (12 ml) at room temperature. To this solution was added *N,N'*-dicyclohexylcarbodiimide (413 mg, 2.00 mmol) and almost immediately precipitation occurs. The mixture was left to stir at room temperature overnight after which it was filtered through Celite and washed with acetonitrile and dichloromethane. The solvent was removed under reduced pressure and re-dissolved in ethyl acetate (75 ml) and washed with 1M HCl, water and brine (50 ml each). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed

under reduced pressure to leave a brown solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:4 → 1:1→ 1:0), to yield a white solid (475 mg, 90%).

Mp 150–154 °C; R_f = 0.25 (Ethyl acetate/heptane, 1:1); IR (ATR): 3772, 3315, 2930, 1669, 1620, 1542,1286, 1101 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 1.41 (s, 9H, –C(CH_3)$_3$), 3.73 (d, *J* = 5.8 Hz, 2H, –CH_2), 6.76 (t, *J* = 7.4 Hz, 1H, Ar–*H*), 6.85–6.94 (m, 2H, Ar–*H*), 7.31 (br t, *J* = 5.3 Hz, 1H, Ar–N*H*), 7.95 (d, *J* = 7.7 Hz, 1H, Ar–*H*), 9.00 (s, 1H, –N*H*), 9.93 (s, 1H, –O*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 28.2 (–C(*C*H_3)$_3$), 44.3 (–*C*H_2), 78.5 (–*C*(CH$_3$)$_3$), 115.1 (Ar–*C*), 119.1 (Ar–*C*), 120.6 (Ar–*C*), 124.2 (Ar–*C*), 126.2 (Ar–*C*), 146.9 (Ar–*C*), 156.0 (*C*=O), 168.3 (*C*=O); HRMS–ESI–: *m/z* $[M–H]^-$ calcd for $C_{13}H_{17}N_2O_4$: 265.1188; found: 265.1191.

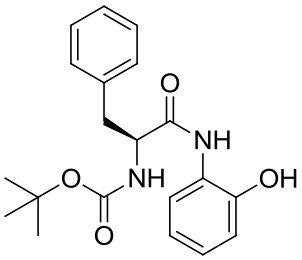
(*S*)-*tert*-Butyl (1-((2-hydroxyphenyl)amino)-1-oxopropan-2-yl)carbamate (5.3)



Boc-*N*-L-alanine (94.6 mg, 0.500 mmol) was dissolved with dichloromethane (4 ml) at room temperature. To this was added 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (101 mg, 0.525 mmol), 1-hydroxybenzotriazole (80.0 mg, 0.525 mmol) and 2-aminophenol (57.0 mg, 0.525 mmol). Lastly was added more dichloromethane (1 ml) and triethylamine (0.14 ml, 1.0 mmol) and the reaction was left to stir at room temperature for 24 hours. The reaction mixture was taken up in ethyl acetate (100 ml) and washed with 1M HCl, H_2O and brine (2x25 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a brown solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 3:22 → 13:87→ 7:43→ 1:1) to yield a mixture of compounds (86 mg). The mixture of compounds were dissolved in tetrahydrofuran (3 ml) and to this was added lithium hydroxide monohydrate (12 mg, 0.50 mmol) in a 1:1 mixture of H_2O and tetrahydrofuran (4 ml). The reaction was left to stir at room temperature until complete as judged by thin layer chromatography (three hours). The reaction was cooled to 0 °C and to this was carefully added 1M HCl (5 ml) and the mixture taken up in ethyl acetate (25 ml), the organic layer separated and further washed with brine (10 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 3:17 → 1:3) to yield a white solid (78 mg, 56%).

Mp 130–134 °C; $[\alpha]_D^{19}$ = –101.6 (*c* 0.40, $CHCl_3$); R_f = 0.33 (Heptane/Ethyl acetate, 9:1); IR (ATR): 3853, 3750, 3339, 3217, 1680, 1657, 1521, 1246, 1061 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 1.27 (d, *J* = 7.1 Hz, 3H, –CH_3), 1.40 (s, 9H, –C(CH_3)$_3$), 4.04–4.22 (m, 1H, –C*H*), 6.76 (t, *J* = 7.2 Hz, 1H, Ar–*H*), 6.82–6.98 (m, 2H, Ar–*H*), 7.38 (d, *J* = 6.0 Hz, 1H, Ar–N*H*), 7.96 (d, *J* = 7.5 Hz, 1H, Ar–*H*), 9.01 (s, 1H, N*H*), 9.92 (s, 1H, O*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 17.5 (–*C*H_3), 28.2 (–C(*C*H_3)$_3$), 50.7 (–*C*H), 78.4 (–*C*(CH$_3$)$_3$), 115.0 (Ar–*C*), 119.0 (Ar–*C*), 120.3 (Ar–*C*), 124.0 (Ar–*C*), 126.3 (Ar–*C*), 146.8 (Ar–*C*), 155.4 (*C*=O), 171.6 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{14}H_{21}N_2O_4$: 281.1501; found: 281.1513.

(S)-tert-Butyl (1-((2-hydroxyphenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (5.4)

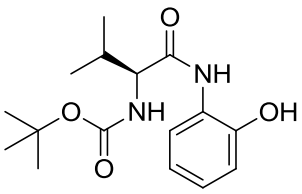


5.4 was synthesised in an analogous method as **5.3**: Boc-*N*-L-phenylalanine (265 mg, 1.00 mmol) was dissolved in dichloromethane (8 ml). To this was added 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (202 mg, 1.05 mmol), 1-hydroxybenzotriazole (160 mg, 1.05 mmol) and 2-aminophenol (115 mg, 1.05 mmol). Lastly was added more dichloromethane (2 ml) and triethylamine (0.28 ml, 2.0 mmol) and the reaction was left to stir at room temperature for 24 hours. The reaction mixture was taken up in ethyl acetate (150 ml) and washed with 1M HCl, H_2O and brine (2x50 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow oil. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 3:7 → 1:0) to yield a white oil (303 mg). The oil was taken up in diethyl ether and hexane and fine white crystals was formed after a few days. The product was filtered off and washed with hexane to yield **5.4** as fine white crystals after drying under high vacuum (250 mg, 70%).

Mp 118–122 °C (diethyl ether/hexane); $[\alpha]_D^{18}$ = –22.0 (*c* 0.09, $CHCl_3$); R_f = 0.52 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3355, 3272, 2930, 1663, 1535, 1451, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.43 (s, 9H, –C(CH_3)$_3$), 3.08–3.23 (m, 2H, –CH_2), 4.56 (d, *J* = 6.0 Hz, 1H, N*H*), 5.14 (d, *J* = 7.1 Hz, 1H, –C*H*), 6.80 (d, *J* = 4.1 Hz, 2H, Ar–*H*), 6.98 (d, *J* = 7.5 Hz, 1H, Ar–*H*), 7.09–7.14 (m, 1H, Ar–*H*), 7.19–7.36 (m, 5H, Ar–*H*), 8.21 (br s, 1H, N*H*), 8.52 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 28.4 (–C(*C*H_3)$_3$), 38.3 (–*C*H_2), 56.6 (–*C*H), 81.4 (–*C*(CH$_3$)$_3$), 119.7 (Ar–*C*), 120.6 (Ar–*C*), 122.7 (Ar–*C*), 125.0 (Ar–*C*), 127.5 (Ar–*C*), 127.5 (Ar–*C*), 129.1 (Ar–*C*), 129.4 (Ar–*C*), 136.1 (Ar–*C*), 149.0 (Ar–*C*), 155.9

(*C*=O), 171.6 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}N_2O_4$: 357.1814; found: 357.1809.

(*S*)-*tert*-Butyl (1-((2-hydroxyphenyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (5.5)

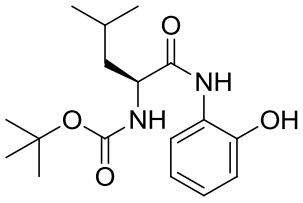


5.5 was synthesised in an analogous method as **5.3**: Boc-*N*-L-valine (217 mg, 1.00 mmol) was dissolved in dichloromethane (8 ml). To this was added 1-ethyl-3-[3-dimethylaminopropyl]-carbodiimide hydrochloride (202 mg, 1.05 mmol), 1-hydroxybenzotriazole (160 mg, 1.05 mmol) and 2-aminophenol (115 mg, 1.05 mmol). Lastly was added more dichloromethane (2 ml) and triethylamine (0.28 ml, 2.0 mmol) and the reaction was left to stir at room temperature for 24 hours. The reaction mixture was taken up in ethyl acetate (150 ml) and washed with 1M HCl, H_2O and brine (2x50 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow oil. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 3:7 → 1:0) to yield a white oil (303 mg). The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 3:22 → 3:17) to yield **5.5** (72 mg) and a mixture of acylated products. The mixture of compounds were dissolved in tetrahydrofuran (4 ml) and to this was added lithium hydroxide monohydrate (24 mg, 1.0 mmol) in a 1:1 mixture of H_2O and tetrahydrofuran (6 ml). The reaction was left to stir at room temperature until complete as judged by thin layer chromatography (five hours). The reaction was cooled to 0 °C and to this was carefully added 1M HCl (10 ml) and the mixture taken up in ethyl acetate (50 ml), the organic layer separated and further washed with brine (10 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 3:17) to yield a white solid **5.5** with a combined yield of (154 mg, 50%).

Mp 114–117 °C; $[\alpha]_D^{21}$ = –43.8 (*c* 0.137, $CHCl_3$); R_f = 0.50 (Heptane/Ethyl acetate, 1:1); IR (ATR): 3360, 3270, 2962, 1665, 1598, 1452, 1295, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.02 (d, *J* = 6.1 Hz, 3H, –CH(CH_3)$_2$), 1.04 (d, *J* = 6.6 Hz, 3H, –CH(CH_3)$_2$), 1.43 (s, 9H, –C(CH_3)$_3$), 2.09–2.26 (m, 1H, –C*H*(CH$_3$)$_2$), 4.15–4.27 (m, 1H, –C*H*), 5.48 (d, *J* = 8.5 Hz, 1H, N*H*), 6.75 (t, *J* = 7.2 Hz, 1H, Ar–*H*), 6.95 (d, *J* = 7.0 Hz, 1H, Ar–*H*), 7.05 (t, *J* = 7.2 Hz, 1H, Ar–*H*), 7.15 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar–*H*), 8.59 and 8.95 (2xbr s, 2x1H, N*H* and O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 18.3 (–*C*H$_3$), 19.5 (–*C*H$_3$), 28.4 (–C(*C*H$_3$)$_3$), 30.9 (–*C*H(CH$_3$)$_2$), 60.9 (–*C*H), 81.0 (–*C*(CH$_3$)$_3$), 119.3 (Ar–*C*), 120.5 (Ar–*C*), 122.6 (Ar–*C*), 125.3

(Ar–*C*), 127.2 (Ar–*C*), 148.8 (Ar–*C*), 156.6 (*C*=O), 172.0 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{16}H_{25}N_2O_4$: 309.1814; found: 309.1823.

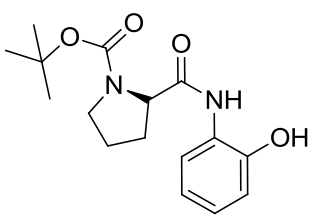
(*S*)-*tert*-Butyl (1-((2-hydroxyphenyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (5.6)



5.6 was synthesised in an analogous method as **5.3**: Boc-*N*-L-leucine (231 mg, 1.00 mmol) was dissolved in dichloromethane (8 ml). To this was added 1-ethyl-3-[3-dimethylaminopropyl]-carbodiimide hydrochloride (202 mg, 1.05 mmol), 1-hydroxybenzotriazole (160 mg, 1.05 mmol) and 2-aminophenol (115 mg, 1.05 mmol). Lastly was added more dichloromethane (2 ml) and triethylamine (0.28 ml, 2.0 mmol) and the reaction was left to stir at room temperature for 22 hours. The reaction mixture was taken up in ethyl acetate (150 ml) and washed with 1M HCl, H_2O and brine (2x50 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave an orange solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: dichloromethane 1:9 → 1:3→ 1:0) to yield an off-white solid. The solid was recrystallised from a mixture of diethyl ether/hexane to yield fine white crystals (194 mg, 60%).

Mp 126–128 °C; $[\alpha]_D^{21}$ = –55.6 (*c* 0.09, $CHCl_3$); R_f = 0.61 (Heptane/Ethyl acetate, 1:1); IR (ATR): 3362, 3277, 2962, 1659, 1598, 1452, 1295, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.95 (d, *J* = 6.9 Hz, 3H, –CH(CH_3)$_2$), 0.98 (d, *J* = 6.7 Hz, 3H, –CH(CH_3)$_2$), 1.47 (s, 9H, –C(CH_3)$_3$), 1.59–1.69 (m, 1H, –CH(CH_3)$_2$), 1.69–1.83 (m, 2H, –CH_2), 4.26–4.49 (m, 1H, –CH), 5.02–5.20 (br, 1H, NH), 6.80 (t, *J* = 7.5 Hz, 1H, Ar–H), 6.98 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.03–7.13 (m, 2H, Ar–H), 8.82 (s, 1H, NH), 8.87 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 23.0 (–CH(CH_3)$_2$), 24.9 (–CH(CH_3)$_2$), 28.4 (–C(CH_3)$_3$), 40.9 (–CH_2), 53.7 (–CH), 81.2 (–C(CH_3)$_3$), 119.3 (Ar–C), 120.3 (Ar–C), 122.3 (Ar–C), 125.3 (Ar–C), 127.1 (Ar–C), 148.6 (Ar–C), 156.4 (C=O), 172.5 (C=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{17}H_{27}N_2O_4$: 323.1971; found: 323.1973.

(*S*)-*tert*-Butyl 2-((2-hydroxyphenyl)carbamoyl)pyrrolidine-1-carboxylate (5.7)

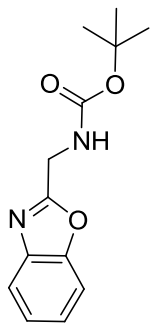


5.7 was synthesised in an analogous method as **5.3**: Boc-*N*-L-proline (215 mg, 1.00 mmol) was dissolved in dichloromethane (8 ml). To this was added 1-ethyl-3-[3-dimethylaminopropyl]-carbodiimide hydrochloride (202 mg, 1.05 mmol), 1-

hydroxybenzotriazole (160 mg, 1.05 mmol) and 2-aminophenol (115 mg, 1.05 mmol). Lastly was added more dichloromethane (2 ml) and triethylamine (0.28 ml, 2.0 mmol) and the reaction was left to stir at room temperature for 24 hours. The reaction mixture was taken up in ethyl acetate (150 ml) and washed with 1M HCl, H_2O and brine (2x50 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellowish solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:3 → 2:3→ 1:0) to yield a white solid after drying under high vacuum (236 mg, 77%). Data corresponded well with literature values.[18]

Mp 132–136 °C; $[\alpha]_D^{20}$ = –148.9 (*c* 0.403, $CHCl_3$); R_f = 0.37 (Heptane/Ethyl acetate, 1:1); IR (ATR): 3666, 3149, 2961, 1658, 1532, 1413, 1366, 1159, 1094, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.44 (s, 9H, –C(C*H*$_3$)$_3$), 1.75–2.46 (m, 4H, –C*H*$_2$), 3.22–3.69 (m, 2H, N–C*H*$_2$), 4.20–4.67 (m, 1H, N–C*H*), 6.69-6.86 (m, 1H, Ar–*H*), 6.87-7.05 (m, 2H, Ar–*H);*7.12-7.35 (m, 1H, Ar–*H)*, 8.45–9.53 (m, 2H, N*H* and O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 24.2 (–*C*H$_2$), 28.3 (–C(*C*H$_3$)$_3$), 31.3 (–*C*H$_2$), 47.2 (N–*C*H$_2$), 61.0 (N–*C*H), 81.3 (–*C*(CH$_3$)$_3$), 117.7 (Ar–*C*), 120.2 (Ar–*C*), 121.6 (Ar–*C*), 125.6 (Ar–*C*), 126.0 (Ar–*C*), 147.8 (Ar–*C*), 155.5 (*C*=O), 172.0 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{16}H_{23}N_2O_4$: 307.1658; found: 307.1656.

tert-Butyl (benzoxazol-2-ylmethyl)carbamate (5.8)

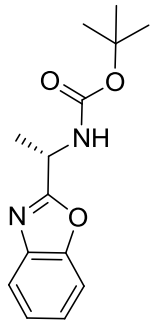


To a solution of **5.2** (466 mg, 1.75 mmol) and triphenylphosphine (550 mg, 2.10 mmol) in tetrahydrofuran (28 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.41 ml, 2.1 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. Thin layer chromatography revealed the reaction to be complete after 24 hours. The solvent was removed under reduced pressure and the solid re-dissolved in ethyl acetate (100 ml) and washed with 1M HCl, water and brine (25 ml each). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave an orange solid. The product was purified twice using flash column chromatography (silica gel eluting with ethyl acetate: heptane 1:9 → 3:17), to yield a white solid (371 mg, 85%).

Mp 84–87 °C; R_f = 0.49 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3347, 2981, 2936, 1690, 1526, 1450, 1241, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.47 (s, 9H, –C(C*H*$_3$)$_3$), 4.62 (d, *J* = 5.5 Hz, 2H, –C*H*$_2$), 5.38 (br s, 1H, N*H*), 7.30–7.36 (m, 2H, Ar–*H*), 7.48–7.54 (m,

1H, Ar–*H*), 7.67–7.71 (m, 1H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 28.5 (–C(*C*H_3)$_3$), 38.7 (–*C*H_2), 80.5 (–*C*(CH$_3$)$_3$), 110.8 (Ar–*C*), 120.0 (Ar–*C*), 124.6 (Ar–*C*), 125.2 (Ar–*C*), 141.0 (Ar–*C*), 151.1 (Ar–*C*), 155.7 (O–*C*=N), 163.5 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}N_2O_3$: 249.1239; found: 249.1242.

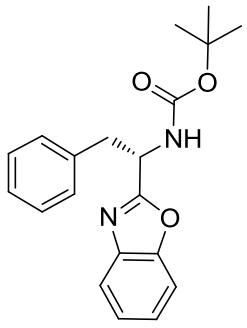
(S)-tert-Butyl (1-(benzoxazol-2-yl)ethyl)carbamate (5.9)



5.9 was synthesised in an analogous method as **5.8**: To a solution of **5.3** (274 mg, 0.980 mmol) and triphenylphosphine (308 mg, 1.18 mmol) in tetrahydrofuran (25 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.230 ml, 1.18 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. Thin layer chromatography revealed the reaction to be complete after 24 hours. The solvent was removed under reduced pressure to yield an orange solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 3:17 → 1:1), to yield a light yellow solid (224 mg, 87%).

Mp 100–104°C; $[\alpha]_D^{21}$ = –62.7 (*c* 0.415, $CHCl_3$); R_f = 0.71 (Heptane/Ethyl acetate, 1:1); IR (ATR): 3346, 2981, 2935, 1764, 1684, 1524, 1452, 1242, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.46 (s, 9H, –C(C*H*$_3$)$_3$), 1.63 (d, *J* = 7.2 Hz, 3H, –C*H*$_3$), 5.06–5.21 (m, 1H, –C*H*), 5.25–5.42 (m, 1H, N*H*),, 7.28–7.37 (m, 2H, Ar–*H*), 7.46–7.55 (m, 1H, Ar–*H*), 7.65–7.74 (m, 1H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 20.4 (–*C*H$_3$), 28.5 (–C(*C*H$_3$)$_3$), 45.4 (–*C*H), 80.3 (–*C*(CH$_3$)$_3$), 110.8 (Ar–*C*), 120.1 (Ar–*C*), 124.6 (Ar–*C*), 125.2 (Ar–*C*), 141.0 (Ar–*C*), 151.0 (Ar–*C*), 155.1 (O–*C*=N), 167.1 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{14}H_{19}N_2O_4$: 263.1396; found: 263.1383.

(S)-tert-Butyl (1-(benzoxazol-2-yl)-2-phenylethyl)carbamate (5.10)

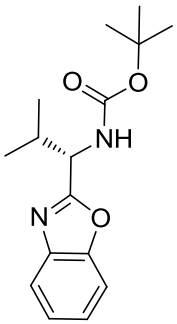


5.10 was synthesised in an analogous method as **5.8**:To a solution of **5.4** (134 mg, 0.376 mmol) and triphenylphosphine (118 mg, 0.450 mmol) in tetrahydrofuran (5 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.090 ml, 0.45 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. Thin layer chromatography revealed the reaction not complete even after 48 hours and more triphenylphosphine (118 mg, 0.450 mmol) and di-isopropyl azodicarboxylate (0.090 ml, 0.45 mmol) were added to the mixture. 52 hours later the reaction was complete according to thin layer chromatography. The solvent was removed under reduced pressure and the product was purified using flash

column chromatography (silica gel eluting with ethyl acetate: hexane 1:19 → 3:17), to yield an off-white solid (111 mg, 87%).

Mp 129–132 °C; $[\alpha]_D^{18}$ = –69.8 (*c* 0.387, $CHCl_3$); R_f = 0.68 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3343, 2981, 2925, 1690, 1527, 1451, 1242, 1164, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.47 (s, 9H, –C(C*H*$_3$)$_3$), 3.25–3.49 (m, 2H, –C*H*$_2$), 5.20 (br s, 1H, N*H*), 5.30–5.45 (m, 1H, –C*H*), 7.02–7.15 (br m, 2H, Ar–*H*), 7.16–7.27 (br m, 3H, Ar–*H*), 7.33–7.46 (m, 2H, Ar–*H*), 7.50–7.60 (m, 1H, Ar–*H*), 7.67–7.77 (m, 1H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 28.4 (–C(*C*H$_3$)$_3$), 40.1 (–*C*H$_2$), 50.5 (–*C*H), 80.2 (–*C*(CH$_3$)$_3$), 110.8 (Ar–*C*), 120.1 (Ar–*C*), 124.6 (Ar–*C*), 125.2 (Ar–*C*), 127.1 (Ar–*C*), 128.6 (Ar–*C*), 129.5 (Ar–*C*), 135.9 (Ar–*C*), 140.9 (Ar–*C*), 150.8 (Ar–*C*), 155.1 (O–*C*=N), 165.7 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_3$: 339.1709; found: 339.1718.

***(S)-tert*-Butyl (1-(benzoxazol-2-yl)-2-methylpropyl)carbamate (5.11)**



5.11 was synthesised in an analogous method as **5.8**: To a solution of **5.5** (146 mg, 0.474 mmol) and triphenylphosphine (370 mg, 1.41 mmol) in tetrahydrofuran (8 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.280 ml, 1.41 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. Thin layer chromatography revealed the reaction to be complete after 22 hours. The solvent was removed under reduced pressure and the product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 2:23 → 1:9→ 1:0), to yield a white solid (116 mg, 85%).

Mp 132–135 °C; $[\alpha]_D^{21}$ = –80.4 (*c* 0.112, $CHCl_3$); R_f = 0.8 (Ethyl acetate/hexane, 3:7); IR (ATR): 3282, 2977, 2928, 1700, 1529, 1458, 1243, 1157, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.97 (d, *J* = 6.4 Hz, 3H, –CH(C*H*$_3$)$_2$), 0.99 (d, *J* = 6.6 Hz, 3H, –CH(C*H*$_3$)$_2$), 1.45 (s, 9H, –C(C*H*$_3$)$_3$), 2.26–2.39 (m, 1H, –C*H*(CH$_3$)$_2$), 4.89–5.00 (m, 1H, –C*H*), 5.36 (br d, *J* = 8.4 Hz, 1H, N*H*), 7.28–7.38 (m, 2H, Ar–*H*), 7.47–7.55 (m, 1H, Ar–*H*), 7.66–7.74 (m, 1H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 18.0 (–*C*H$_3$), 19.0 (–*C*H$_3$), 28.4 (–C(*C*H$_3$)$_3$), 32.9 (–*C*(CH$_3$)$_2$), 54.8 (–*C*H), 80.1 (–*C*(CH$_3$)$_3$), 110.8 (Ar–*C*), 120.1 (Ar–*C*), 124.5 (Ar–*C*), 125.1 (Ar–*C*), 140.8 (Ar–*C*), 150.7 (Ar–*C*), 155.6 (O–*C*=N), 166.5 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{16}H_{23}N_2O_3$: 291.1709; found: 291.1703

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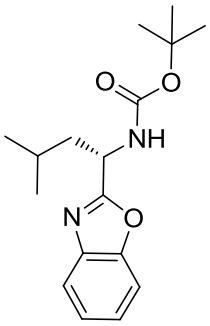
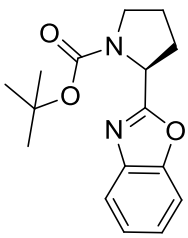
(S)-tert-Butyl (1-(benzoxazol-2-yl)-3-methylbutyl)carbamate (5.12)



5.12 was synthesised in an analogous method as **5.8**: To a solution of **5.6** (104 mg, 0.323 mmol) and triphenylphosphine (102 mg, 0.390 mmol) in tetrahydrofuran (5 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.080 ml, 0.39 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. Thin layer chromatography revealed the reaction to be complete after 26 hours. The solvent was removed under reduced pressure and the product was purified twice using flash column chromatography (silica gel eluting with ethyl acetate: heptane 3:17 and silica gel eluting with ethyl acetate: heptane 1:9), to yield an off-white solid (88 mg, 90%).

Mp 70–73 °C; $[\alpha]_D^{19}$ = –66.1 (*c* 0.268, $CHCl_3$); R_f = 0.60 (Heptane/Ethyl acetate, 7:3); IR (ATR): 3350, 2967, 1688, 1525, 1452, 1241, 1166, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.90–0.99 (m, 6H, –CH(CH_3)$_2$), 1.45 (s, 9H, –C(CH_3)$_3$), 1.69–1.88 (m, 3H, –C*H*(CH_3)$_2$ and –CH_2), 5.09–5.17 (m, 1H, –C*H*), 5.36 (d, *J* = 7.9 Hz, 1H, N*H*), 7.28–7.34 (m, 2H, Ar–*H*), 7.47–7.53 (m, 1H, Ar–*H*), 7.67–7.72 (m, 1H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 22.2 (–CH_3), 22.8 (–CH_3), 24.8 (–*C*H(CH_3)$_2$), 28.4 (–C(CH_3)$_3$), 43.6 (–CH_2), 47.9 (–*C*H), 80.0 (–*C*(CH_3)$_3$), 110.7 (Ar–*C*), 120.0 (Ar–*C*), 124.4 (Ar–*C*), 125.0 (Ar–*C*), 141.0 (Ar–*C*), 150.7 (Ar–*C*), 155.3 (O–*C*=N), 167.1 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{17}H_{25}N_2O_3$: 305.1865; found: 305.1859.

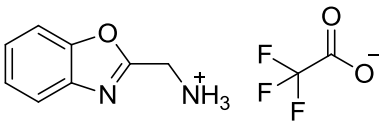
(S)-tert-Butyl 2-(1,3-benzoxazol-2-yl)pyrrolidine-1-carboxylate (5.13)



5.13 was synthesised in an analogous method as **5.8**: To a solution of **5.7** (324 mg, 1.06 mmol) and triphenylphosphine (333 mg, 1.27 mmol) in tetrahydrofuran (18 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.250 ml, 1.27 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. Thin layer chromatography revealed the reaction not complete after 27 hours and more triphenylphosphine (500 mg, 1.91 mmol) and di-isopropyl azodicarboxylate (0.380 ml, 1.91 mmol) were added to the mixture. 15 hours later the reaction was complete according to thin layer chromatography. The solvent was removed under reduced pressure and the product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:9 → 3:17→ 3:7→ 1:0), to yield a white oil that slowly solidified (145 mg, 48%).

Mp 87–90 °C; $[\alpha]_D^{21}$ = –103.7 (*c* 0.135, $CHCl_3$); R_f = 0.46 (Ethyl acetate/hexane, 3:7); IR (ATR): 2976, 2886, 1689, 1451, 1392, 1241, 1153, 1113, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.20 and 1.45 (2xs, 9H, –C*H*$_3$), 1.91–2.48 (m, 4H, –C*H*$_2$), 3.45–3.78 (m, 2H, N–C*H*$_2$), 4.98–5.20 (m, 1H, N–C*H*), 7.27–7.37 (m, 2H, Ar–*H*), 7.45–7.53 (m, 1H, Ar–*H*), 7.65–7.73 (m, 1H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 23.9 (–*C*H$_2$), 28.2 and 28.5 (–*C*H$_3$), 32.7 (–*C*H$_2$), 46.8 (N–*C*H$_2$), 55.3 (N–*C*H), 80.1 (–*C*(CH$_3$)$_3$), 110.6 (Ar–*C*), 120.0 (Ar–*C*), 124.5 (Ar–*C*), 125.0 (Ar–*C*), 141.1 (Ar–*C*), 150.6 (Ar–*C*), 154.0 (O–*C*=N), 167.6 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}N_2O_3$: 289.1552; found: 289.1552.

2-Aminomethyl-1,3-benzoxazole trifluoroacetate (5.14)*

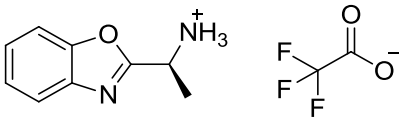


Trifluoroacetic acid (0.50 ml, 6.3 mmol) was added to a solution of **5.8** (157 mg, 0.630 mmol) in dichloromethane (4 ml) at room temperature. The reaction was followed to completion by thin layer chromatography (three hours) and the solvent removed under reduced pressure to leave a colourless oil. The oil was taken up in heptane (5 ml) and diethyl ether was added until a precipitate was formed. The white precipitate was collected and dried under high vacuum to yield **5.14** (132 mg, 80%).

Mp 151–156 °C; R_f = 0.35 (methanol/dichloromethane, 1:19); IR (ATR): 3270, 3058, 2633, 1674, 1554, 1446, 1181, 1128, 1042 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 4.52 (s, 2H, –C*H*$_2$), 7.41–7.50 (m, 2H, Ar–*H*), 7.77–7.82 (m, 2H, Ar–*H*), 8.81 (br s, 3H, N*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 36.2 (–*C*H$_2$), 111.0 (Ar–*C*), 119.8 (Ar–*C*), 125.1 (Ar–*C*), 125.9 (Ar–*C*), 140.0 (Ar–*C*), 150.3 (Ar–*C*), 158.2 (q, $J_{C\text{-}F}$ = 32.0 Hz,CF_3–*C*=O), 160.3 (O–*C*=N); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_8H_9N_2O$: 149.0715; found: 149.0717;

* During this study it was found that the assignment of the TFA salt in ^{13}C NMR spectroscopy was very challenging for these and the 4-hydroxybenzoxazole salts. Due to the large splitting pattern ($J_{C\text{-}F}$ ~300 Hz for CF_3 signal and $J_{C\text{-}F}$ ~ 30 Hz for carbonyl signal), caused by the C-F interaction, the signals were lost in the baseline of the spectra. In most of the cases the carbonyl carbon could be assigned, but not the CF_3 signal. See ^{13}C NMR spectrum at end of section as an indication of the relative amplitude and position of these chemical signals.

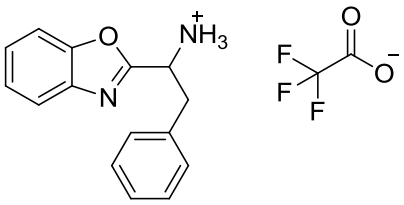
(*S*)-2-(1-Aminoethyl)-1,3-benzoxazole trifluoroacetate (5.15)



Trifluoroacetic acid (0.40 ml, 5.2 mmol) was added to a solution of **5.9** (135 mg, 0.515 mmol) in dichloromethane (3 ml) at room temperature. The reaction was followed to completion by thin layer chromatography (three hours) and the solvent removed under reduced pressure to leave a colourless oil. The oil was taken up in hexane (5 ml) and diethyl ether was added until a precipitate was formed. The white precipitate was collected and dried under high vacuum to yield **5.15** (109 mg, 77%).

Mp 145–148 °C; $[\alpha]_D^{21}$ = –19.0 (*c* 0.105, MeOH); R_f = 0.39 (Methanol/dichloromethane, 1:19); IR (ATR): 3463, 3282, 2944, 1661, 1519, 1453, 1181, 1141, 1004 cm^{-1}; ^{1}H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 1.68 (d, *J* = 6.9 Hz, 3H, –C*H*$_3$), 4.91 (q, *J* = 6.9 Hz, 1H, –C*H*), 7.35–7.55 (m, 2H, Ar–*H*), 7.69–7.88 (m, 2H, Ar–*H*), 9.00 (br s, 3H, N*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 17.0 (–*C*H$_3$), 44.2 (–*C*H), 111.1 (Ar–*C*), 120.0 (Ar–*C*), 125.1 (Ar–*C*), 126.0 (Ar–*C*), 140.0 (Ar–*C*), 150.3 (Ar–*C*), 158.4 (q, $J_{C\text{-}F}$ = 31.5 Hz,CF_3–*C*(O)), 163.2 (O–*C*=N); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_9H_{11}N_2O$: 163.0871; found: 163.0881;

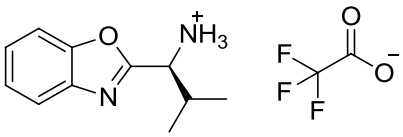
(*Rac*)-2-(1-Amino-2-phenylethyl)-1,3-benzoxazole trifluoroacetate (5.16)



Trifluoroacetic acid (0.17 ml, 2.2 mmol) was added to a solution of **5.10** (73.2 mg, 0.216 mmol) in dichloromethane (2 ml) at room temperature. The reaction was followed to completion by thin layer chromatography (three hours) and the solvent removed under reduced pressure to leave a colourless oil. The oil was taken up in hexane (2 ml) and diethyl ether was added until a precipitate was formed. The white precipitate was collected and dried under high vacuum to yield **5.16** (59 mg, 77%).

Mp 122–124 °C; R_f = 0.44 (methanol/dichloromethane, 1:19); IR (ATR): 3696, 3370, 3062, 2450, 1687, 1453, 1195, 1135, 975 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 3.38–3.57 (m, 2H, –C*H*$_2$), 4.99–5.08 (m, 1H, –C*H*), 7.12–7.23 (m, 2H, Ar–*H*), 7.23–7.34 (m, 3H, Ar–*H*), 7.37–7.50 (m, 2H, Ar–*H*), 7.59–7.66 (m, 1H, Ar–*H*), 7.69–7.76 (m, 1H, Ar–*H*); ^{13}C NMR (CD_3OD, 75.5 MHz, 25 °C): δ = 39.1 (–*C*H$_2$), 51.64 (–*C*H), 112.0 (Ar–*C*), 121.3 (Ar–*C*), 126.3 (Ar–*C*), 127.4 (Ar–*C*), 128.9 (Ar–*C*), 130.1 (Ar–*C*), 130.4 (Ar–*C*), 135.2 (Ar–*C*), 141.6 (Ar–*C*), 152.3 (Ar–*C*), 162.6 (O–*C*=N); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}N_2O$: 239.1184; found: 239.1195.

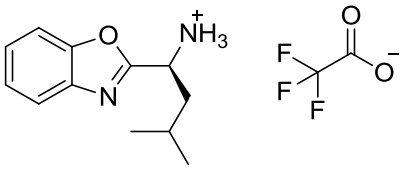
(*S*)-2-(1-Amino-2-methylpropyl)-1,3-benzoxazole trifluoroacetate (5.17)



Trifluoroacetic acid (0.07 ml, 0.9 mmol) was added to a solution of **5.11** (26.5 mg, 0.0900 mmol) in dichloromethane (1 ml) at room temperature. The reaction was followed to completion by thin layer chromatography (three hours) and the solvent removed under reduced pressure to leave a colourless oil. The oil was taken up in hexane (2 ml) and diethyl ether was added until a precipitate was formed. The white precipitate was collected and dried under high vacuum to yield **5.17** (25 mg, 91%).

Mp 109–111 °C; $[\alpha]_D^{25}$ = –50.6 (*c* 0.079, MeOH); R_f = 0.42 (methanol/dichloromethane, 1:19); IR (ATR): 3618, 3373, 2930, 1666, 1512, 1181, 1134, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 1.02 (d, *J* = 6.5 Hz, 3H, –C*H*$_3$), 1.12 (d, *J* = 6.5 Hz, 3H, –C*H*$_3$), 2.49–2.60 (m, 1H, –C*H*$(CH_3)_2$), 4.55 (br d, *J* = 3.6 Hz, 1H, –C*H*), 7.29–7.39 (m, 2H, Ar–*H*), 7.50 (d, *J* = 7.5 Hz, 1H, Ar–*H*), 7.68 (d, *J* = 7.2 Hz, 1H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 17.7 (–*C*H_3), 18.5 (–*C*H_3), 31.5 (–*C*H$(CH_3)_2$), 55.1 (–*C*H), 111.1 (Ar–*C*), 120.5 (Ar–*C*), 125.1 (Ar–*C*), 126.1 (Ar–*C*), 140.0 (Ar–*C*), 151.0 (Ar–*C*), 161.0 (O–*C*=N); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{11}H_{15}N_2O$: 191.1184; found: 191.1193.

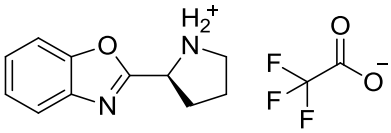
(*S*)-2-(1-Amino-3-methylbutyl)-1,3-benzoxazole trifluoroacetate (5.18)



Trifluoroacetic acid (0.20 ml, 2.6 mmol) was added to a solution of **5.12** (79.3 mg, 0.260 mmol) in dichloromethane (2.5 ml) at room temperature. The reaction was followed to completion by thin layer chromatography (four hours) and the solvent removed under reduced pressure to leave a colourless oil. The oil was taken up in hexane (3 ml) and diethyl ether was added until a precipitate was formed. The white precipitate was collected and dried under high vacuum to yield **5.18** (69 mg, 83%).

Mp 156–158 °C; $[\alpha]_D^{21}$ = –40 (*c* 0.100, MeOH); R_f = 0.42 (methanol/dichloromethane, 1:19); IR (ATR): 3700, 3648, 2955, 1664, 1504, 1186, 1139, 835 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 0.90 (d, *J* = 6.5 Hz, 3H, –C*H*$_3$), 0.93 (d, *J* = 6.6 Hz, 3H, –C*H*$_3$), 1.55–1.76 (m, 1H, –C*H*$(CH_3)_2$), 1.77–2.09 (m, 2H, –C*H*$_2$), 4.80 (dd, *J* = 8.2, 6.5 Hz, 1H, –C*H*), 7.37–7.59 (m, 2H, Ar–*H*), 7.70–7.95 (m, 2H, Ar–*H*), 8.87 (s, 3H, N*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 21.8 (–*C*H_3), 22.3 (–*C*H_3), 24.0 (–*C*H$(CH_3)_2$), 40.5 (–*C*H_2), 46.9 (–*C*H), 111.2 (Ar–*C*), 120.0 (Ar–*C*), 125.2 (Ar–*C*), 126.1 (Ar–*C*), 139.9 (Ar–*C*), 150.2 (Ar–*C*), 162.6 (O–*C*=N); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{12}H_{17}N_2O$: 205.1341; found: 205.1351.

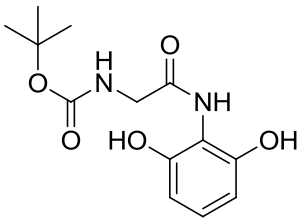
(*S*)-2-(Pyrrolidin-2-yl)-1,3-benzoxazole trifluoroacetate (5.19)



Trifluoroacetic acid (0.21 ml, 2.8 mmol) was added to a solution of **5.13** (81.6 mg, 0.280 mmol) in dichloromethane (3 ml) at room temperature. The reaction was followed to completion by thin layer chromatography (six hours) and the solvent removed under reduced pressure to leave a brownish oil. The oil was taken up in hexane (2 ml) and diethyl ether was added until a precipitate was formed. The light brown precipitate was collected and dried under high vacuum to yield **5.19** (51 mg, 60%).

Mp 146–148°C(dec); $[\alpha]_D^{29}$ = –5.7 (*c* 0.176, MeOH); R_f = 0.15 (methanol/dichloromethane, 1:19); IR (ATR): 3301, 3222, 2896, 2575, 1663, 1599, 1546, 1455, 1182, 1045 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 1.85–2.01 (m, 2H, –CH_2), 2.31–2.46 (m, 2H, –CH_2), 3.16–3.34 (m, 2H, N–CH_2), 4.44–4.55 (m, 1H, N–C*H*), 6.74–6.84 (m, 1H, Ar–*H*), 6.87–6.94 (m, 1H, Ar–*H*), 6.95–7.04 (m, 1H, Ar–*H*), 7.80 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar–*H*), 9.81 (s, 1H, N*H*), 10.02 (s, 1H, N*H*); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{11}H_{13}N_2O$: 189.1028; found: 189.1024.

***tert*-Butyl (2-((2,6-dihydroxyphenyl)amino)-2-oxoethyl)carbamate (5.20)**

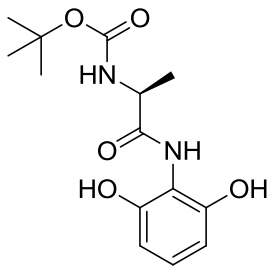


N-Boc-glycine (176 mg, 1.00 mmol) and 2-aminoresorcinol **2.2** (125 mg, 1.00 mmol) was dissolved in acetonitrile (6 ml) at room temperature. To this solution was added *N,N'*-Dicyclohexylcarbodiimide (206 mg, 1.00 mmol) and almost immediately precipitation occurs. The mixture was left to stir at room temperature overnight after which it was filtered through Celite and washed with acetonitrile and dichloromethane. The solvent was removed under reduced pressure and re-dissolved in ethyl acetate (75 ml) and washed with 1M HCl, water and brine (25 ml each). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a brown solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: dichloromethane 1:9 → 1:4→ 3:7), to yield a white solid (225 mg, 80%).

Mp 172–174 °C (dec); R_f = 0.31 (Ethyl acetate/heptane, 3:7); IR (ATR): 3747, 3705, 3294, 3222, 2985, 1686, 1653, 1541, 1275, 1156 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 1.40 (s, 9H, –C(CH_3)$_3$), 3.82 (d, *J* = 5.7 Hz, 2H, –CH_2), 6.35 (d, *J* = 8.1 Hz, 2H, Ar–*H*), 6.87 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 7.16 (br t, *J* = 5.2 Hz, 1H, N*H*), 9.14 (s, 1H, N*H*), 9.43 (s, 2H, O*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 28.2 (–C(*C*H_3)$_3$), 43.5 (–*C*H_2), 78.4 (–*C*(CH$_3$)$_3$),

107.5 (Ar–*C*), 113.3 (Ar–*C*), 126.7 (Ar–*C*), 151.7 (Ar–*C*), 155.9 (*C*=O), 169.9 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_5$: 283.1294; found: 283.1293.

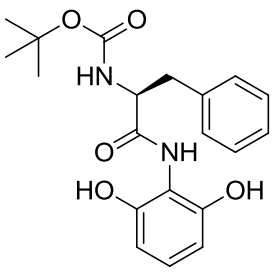
(*S*)-*tert*-Butyl (1-((2,6-dihydroxyphenyl)amino)-1-oxopropan-2-yl)carbamate (5.21)



Boc-*N*-L-alanine (189 mg, 1.00 mmol) was dissolved with dimethylformamide (8 ml) at room temperature. To this was added 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (202 mg, 1.05 mmol), 1-hydroxybenzotriazole (160 mg, 1.05 mmol) and 2-aminoresorcinol **2.2** (131 mg, 1.05 mmol). Lastly was added more dimethylformamide (2 ml) and the reaction was left to stir at room temperature for 22 hours. The reaction mixture was taken up in ethyl acetate (100 ml) and washed with 1M HCl, H_2O and brine (2x25 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a brown solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 1:3 → 3:7) to yield a small amount of **5.21** and a mixture of compounds. The mixture of compounds were dissolved in tetrahydrofuran (4 ml) and to this was added lithium hydroxide monohydrate (14 mg, 0.60 mmol) in a 1:1 mixture of H_2O and tetrahydrofuran (4 ml). The reaction was left to stir at room temperature until complete as judged by thin layer chromatography (one hour). The reaction was cooled to 0 °C and to this was carefully added 1M HCl (5 ml) and the mixture taken up in ethyl acetate (25 ml), the organic layer separated and further washed with brine (10 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 1:4 → 1:3→ 1:1) to yield a white solid (184 mg, 62% combined).

Mp 100–104 °C; $[\alpha]_D^{19}$ = –59.6 (*c* 0.496, $CHCl_3$); R_f = 0.41 (Heptane/Ethyl acetate, 1:1); IR (ATR): 3300, 2930, 1688, 1654, 1533, 1311, 1264, 1158, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.47 (s, 9H, –C(C*H*$_3$)$_3$), 1.49 (t, *J* = 7.3 Hz, 3H, –C*H*$_3$), 4.32-4.47 (m, 1H, –C*H*), 5.21 (d, *J* = 7.1 Hz, 1H, N*H*), 6.48 (d, *J* = 8.1 Hz, 2H, Ar–*H*), 6.91 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 8.48 (br s, 1H, N*H*), 8.57 (br s, 2H, O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 18.4 (–*C*H$_3$), 28.4 (–C(*C*H$_3$)$_3$), 50.9 (–*C*H), 81.6 (–*C*(CH$_3$)$_3$), 109.3 (Ar–*C*), 114.3 (Ar–*C*), 127.1 (Ar–*C*), 149.1 (Ar–*C*), 156.2 (*C*=O), 172.8 (*C*=O); HRMS–ESI–: *m/z* $[M-H]^-$ calcd for $C_{14}H_{19}N_2O_5$: 295.1294; found: 295.1290.

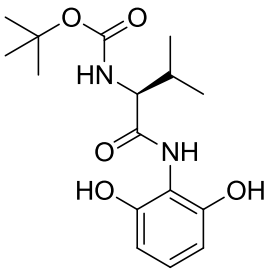
(S)-tert-Butyl (1-((2,6-dihydroxyphenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (5.22)



5.22 was synthesised in an analogous method as **5.21**: Boc-*N*-L-phenylalanine (265 mg, 1.00 mmol) was dissolved in dimethylformamide (10 ml). To this was added 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (202 mg, 1.05 mmol), 1-hydroxybenzotriazole (160 mg, 1.05 mmol) and 2-aminoresorcinol **2.2** (131 mg, 1.05 mmol) and the reaction was left to stir at room temperature for 21 hours. The reaction mixture was taken up in ethyl acetate (100 ml) and washed with 1M HCl, H_2O and brine (2x25 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a brown solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 1:3 → 1:1) to yield a mixture of compounds. These were dissolved in tetrahydrofuran (4 ml) and to this was added lithium hydroxide monohydrate (12 mg, 0.50 mmol) in a 1:1 mixture of H_2O and tetrahydrofuran (4 ml). The reaction was left to stir at room temperature until complete as judged by thin layer chromatography (two hours). The reaction was cooled to 0 °C and to this was carefully added 1M HCl (5 ml) and the mixture taken up in ethyl acetate (25 ml), the organic layer separated and further washed with brine (10 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 1:3 → 1:1) to yield an off-white solid (260 mg, 70%).

Mp 138–140 °C; $[\alpha]_D^{19}$ = –27.7 (*c* 0.556, $CHCl_3$); R_f = 0.30 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3286, 3226, 2933, 1687, 1600, 1534, 1257, 1159, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 1.48 (s, 9H, –C(C*H*$_3$)$_3$), 3.10–3.34 (m, 2H, –C*H*$_2$), 4.55-4.70 (m, 1H, –C*H*), 5.31 (br s, 1H, N*H*), 6.54 (d, *J* = 8.1 Hz, 2H, Ar–*H*), 6.99 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 7.22–7.28 (m, 2H, Ar–*H*), 7.28–7.39 (m, 3H, Ar–*H*), 8.45 (br s, 3H, O*H* and N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 28.3 (–C(*C*H$_3$)$_3$), 38.4 (–*C*H$_2$), 56.4 (–*C*H), 81.7 (–*C*(CH$_3$)$_3$), 109.3 (Ar–*C*), 114.1 (Ar–*C*), 127.3 (Ar–*C*), 127.5 (Ar–*C*), 129.0 (Ar–*C*), 129.3 (Ar–*C*), 135.7 (Ar–*C*), 149.3 (Ar–*C*), 156.2 (*C*=O), 171.4 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}N_2O_5$: 373.1763; found: 373.1765.

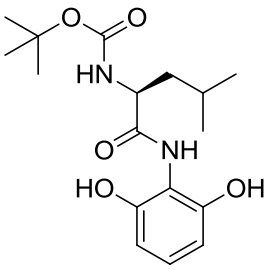
(*S*)-*tert*-Butyl (1-((2,6-dihydroxyphenyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (5.23)



5.23 was synthesised in an analogous method as **5.21**: Boc-*N*-L-valine (217 mg, 1.00 mmol) was dissolved in dimethylformamide (10 ml). To this was added 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (202 mg, 1.05 mmol), 1-hydroxybenzotriazole (160 mg, 1.05 mmol) and 2-aminoresorcinol **2.2** (131 mg, 1.05 mmol) and the reaction was left to stir at room temperature for 21 hours. The reaction mixture was taken up in ethyl acetate (150 ml) and washed with 1M HCl, H_2O and brine (2x50 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave an orange solid. The solid was dissolved in tetrahydrofuran (4 ml) and to this was added lithium hydroxide monohydrate (24 mg, 1.0 mmol) in a 1:1 mixture of H_2O and tetrahydrofuran (6 ml). The reaction was left to stir at room temperature until complete as judged by thin layer chromatography (three hours). The reaction was cooled to 0 °C and to this was carefully added 1M HCl (10 ml) and the mixture taken up in ethyl acetate (50 ml), the organic layer separated and further washed with brine (10 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 3:17→ 1:4) to yield a white solid (124 mg, 38%).

Mp 178–180 °C; $[\alpha]_D^{24}$ = –22.2 (*c* 0.135, $CHCl_3$); R_f = 0.27 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3368, 3291, 2971, 1671, 1594, 1514, 1272, 1156, 1036 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 0.86–0.98 (m, 6H, –CH(C*H*$_3$)$_2$), 1.40 (s, 9H, –C(C*H*$_3$)$_3$), 1.99–2.11 (m, 1H, –C*H*(CH$_3$)$_3$), 4.09 (br t, *J* = 7.3 Hz, 1H, –C*H*), 6.35 (d, *J* = 8.1 Hz, 2H, Ar–*H*), 6.88 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 6.96 (d, *J* = 8.1 Hz, 1H, N*H*), 9.23 (br s, 1H, N*H*), 9.42 (br s, 2H, O*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 18.1 (–*C*H$_3$), 19.2 (–*C*H$_3$), 28.2 (–C(*C*H$_3$)$_3$), 30.4 (–*C*H(CH$_3$)$_2$), 59.9 (–*C*H), 78.3 (–*C*(CH$_3$)$_3$), 107.5 (Ar–*C*), 113.4 (Ar–*C*), 126.7 (Ar–*C*), 151.9 (Ar–*C*), 155.7 (*C*=O), 171.9 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{16}H_{25}N_2O_5$: 325.1763; found: 325.1762.

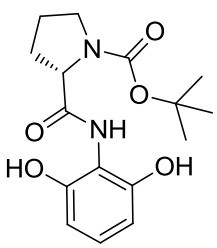
(*S*)-*tert*-Butyl (1-((2,6-dihydroxyphenyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (5.24)



5.24 was synthesised in an analogous method as **5.21**: Boc-*N*-L-leucine (231 mg, 1.00 mmol) was dissolved in dimethylformamide (10 ml). To this was added 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (202 mg, 1.05 mmol), 1-hydroxybenzotriazole (160 mg, 1.05 mmol) and 2-aminoresorcinol **2.2** (131 mg, 1.05 mmol) and the reaction was left to stir at room temperature for 20 hours. The reaction mixture was taken up in ethyl acetate (150 ml) and washed with 1M HCl, H_2O and brine (2x50 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave an orange solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 1:9 → 3:17→ 1:0) to yield a mixture of compounds. These were dissolved in tetrahydrofuran (4 ml) and to this was added lithium hydroxide monohydrate (12 mg, 0.50 mmol) in a 1:1 mixture of H_2O and tetrahydrofuran (4 ml). The reaction was left to stir at room temperature until complete as judged by thin layer chromatography (three hours). The reaction was cooled to 0 °C and to this was carefully added 1M HCl (5 ml) and the mixture taken up in ethyl acetate (25 ml), the organic layer separated and further washed with brine (10 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 1:9 → 3:17) to yield an off-white solid (209 mg, 62%).

Mp 67–70 °C; $[\alpha]_D^{19}$ = –58.9 (*c* 0.526, $CHCl_3$); R_f = 0.30 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3365, 3321, 2958, 1688, 1599, 1533, 1366, 1160, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.90–0.99 (m, 6H, –CH(C*H*$_3$)$_2$), 1.46 (s, 9H, –C(C*H*$_3$)$_3$), 1.56–1.81 (m, 3H, –C*H*$_2$ and –C*H*(CH$_3$)$_2$), 4.29-4.45 (m, 1H, –C*H*), 5.37 (br s, 1H, N*H*), 6.47 (d, *J* = 8.2 Hz, 2H, Ar–*H*), 6.89 (t, *J* = 8.2 Hz, 1H, Ar–*H*), 8.61 (br s, 1H, N*H*), 9.14 (br s, 2H, O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 22.9 (–CH(*C*H$_3$)$_2$), 24.9 (–*C*H(CH$_3$)$_2$), 28.4 (–C(*C*H$_3$)$_3$), 41.3 (–*C*H$_2$), 53.8 (–*C*H), 81.6 (–*C*(CH$_3$)$_3$), 109.1 (Ar–*C*), 114.2 (Ar–*C*), 127.1 (Ar–*C*), 149.2 (Ar–*C*), 156.5 (*C*=O), 172.6 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{17}H_{27}N_2O_5$: 339.1920; found: 339.1918.

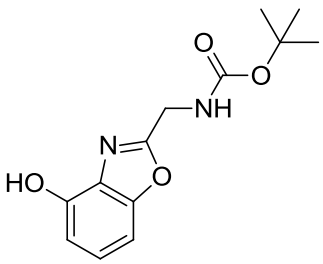
(*S*)-*tert*-butyl 2-((2,6-dihydroxyphenyl)carbamoyl)pyrrolidine-1-carboxylate (5.25)



5.25 was synthesised in an analogous method as **5.21:** Boc-*N*-L-proline (215 mg, 1.00 mmol) was dissolved in dimethylformamide (10 ml). To this was added 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (202 mg, 1.05 mmol), 1-hydroxybenzotriazole (160 mg, 1.05 mmol) and 2-aminoresorcinol **2.2** (131 mg, 1.05 mmol) and the reaction was left to stir at room temperature for 22 hours. The reaction mixture was taken up in ethyl acetate (150 ml) and washed with 1M HCl, H_2O and brine (2x50 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid. This was dissolved in tetrahydrofuran (4 ml) and to this was added lithium hydroxide monohydrate (24 mg, 1.0 mmol) in a 1:1 mixture of H_2O and tetrahydrofuran (6 ml). The reaction was left to stir at room temperature until complete as judged by thin layer chromatography (four hours). The reaction was cooled to 0 °C and to this was carefully added 1M HCl (10 ml) and the mixture taken up in ethyl acetate (50 ml), the organic layer separated and further washed with brine (10 ml). The organic phase was dried over anhydrous magnesium sulfate, the drying agent was filtered off and the solvent removed under reduced pressure to leave a yellow solid. The product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 1:3 → 7:13) to yield an off-white solid (145 mg, 45%).

Mp 146–150 °C; $[\alpha]_D^{21}$ = –97.7 (*c* 0.133, $CHCl_3$); R_f = 0.25 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3323, 3154, 2932, 1659, 1598, 1542, 1396, 1258, 1159, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.43 (s, 9H, –C(C*H*$_3$)$_3$), 1.83–2.42 (m, 4H, –C*H*$_2$), 3.38–3.65 (m, 2H, N–C*H*$_2$), 4.36–4.57 (m, 1H, N–C*H*), 6.43–6.62 (m, 2H, Ar–*H*), 6.85–6.98 (m, 1H, Ar–*H*), 8.56–8.78 (m, 1H, N*H*), 9.44 (br s, 2H, O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 23,8 (–*C*H$_2$), 28.3 (–C(*C*H$_3$)$_3$), 31.4 (–*C*H$_2$), 47.2 (N–*C*H$_2$), 61.9 (N–*C*H), 82.5 (–*C*(CH$_3$)$_3$), 108.7 (Ar–*C*), 109.0 (Ar–*C*), 114.0 (Ar–*C*), 126.8 (Ar–*C*), 149.0 (Ar–*C*), 155.5 (Ar–*C*), 157.4 (*C*=O), 172.4 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{16}H_{23}N_2O_5$: 323.1607; found: 323.1618.

***tert*-Butyl ((4-hydroxy-1,3-benzoxazol-2-yl)methyl)carbamate (5.26)**

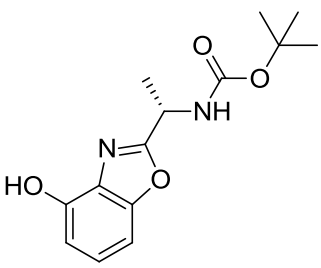


To a solution of **5.20** (187 mg, 0.660 mmol) and triphenylphosphine (871 mg, 3.32 mmol) in tetrahydrofuran (10 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.650 ml, 3.32 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature.

Thin layer chromatography revealed the reaction to be complete after two hours. The solvent was removed under reduced pressure and the product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 3:17 → 1:3→ 1:1), to yield a white solid (148 mg, 85%).

Mp 175–178 °C (dec); R_f = 0.38 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3363, 3147, 2985, 1639, 1614, 1525, 1450, 1247, 1163, 1045 cm^{-1}; ^1H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 1.40 (s, 9H, –C(CH_3)$_3$), 4.39 (d, *J* = 5.9 Hz, 2H, –CH_2), 6.72 (d, *J* = 7.8 Hz, 1H, Ar–*H*), 7.07 (d, *J* = 8.0 Hz, 1H, Ar–*H*), 7.15 (t, *J* = 8.0 Hz, 1H, Ar–*H*), 7.60 (t, *J* = 5.8 Hz, 1H, N*H*), 10.23 (s, 1H, O*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 28.2 (–C(*C*H_3)$_3$), 37.8 (–*C*H_2), 78.5 (–*C*(CH_3)$_3$), 101.3 (Ar–*C*), 110.2 (Ar–*C*), 125.5 (Ar–*C*), 129.4 (Ar–*C*), 149.2 (Ar–*C*), 152.0 (Ar–*C*), 155.6 (O–*C*=N), 162.0 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}N_2O_4$: 265.1188; found: 265.1201.

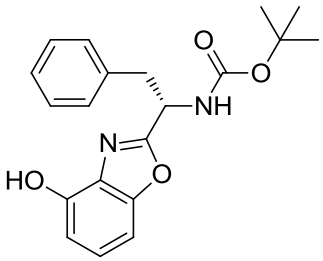
(*S*)-*tert*-Butyl (1-(4-hydroxy-1,3-benzoxazol-2-yl)ethyl)carbamate (5.27)



5.27 was synthesised in an analogous method as **5.26**: To a solution of **5.21** (138 mg, 0.470 mmol) and triphenylphosphine (611 mg, 3.33 mmol) in tetrahydrofuran (8 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.460 ml, 3.33 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. Thin layer chromatography revealed the reaction to be complete after four hours. The solvent was removed under reduced pressure and the product was purified twice using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:19 → 1:9→ 3:22→ 1:4 followed by silica gel eluting with ethyl acetate: dichloromethane 1:19 → 3:37→ 1:9→ 1:4), to yield a white solid (79mg, 60%).

Mp 72–75 °C; $[\alpha]_D^{21}$ = –106.2 (*c* 0.113, $CHCl_3$); R_f = 0.42 (Heptane/Ethyl acetate, 1:1); IR (ATR): 3399, 3340, 2981, 1690, 1618, 1503, 1451, 1246, 1159, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.33 (s, 9H, –C(CH_3)$_3$), 1.61 (d, *J* = 7.0 Hz, 3H, –CH_3), 5.07–5.21 (m, 1H, –C*H*), 5.99 (br d, *J* = 7.1 Hz, 1H, N*H*), 6.88 (d, *J* = 8.1 Hz, 1H, Ar–*H*), 7.03 (d, *J* = 8.1 Hz, 1H, Ar–*H*), 7.20 (t, *J* = 8.1 Hz, 1H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 20.5 (–*C*H_3), 28.3 (–C(*C*H_3)$_3$), 45.3 (–*C*H), 80.2 (–*C*(CH_3)$_3$), 102.5 (Ar–*C*), 111.4 (Ar–*C*), 126.3 (Ar–*C*), 128.9 (Ar–*C*), 148.1 (Ar–*C*), 151.9 (Ar–*C*), 155.3 (O–*C*=N), 166.5 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{14}H_{19}N_2O_4$: 279.1345; found: 279.1333.

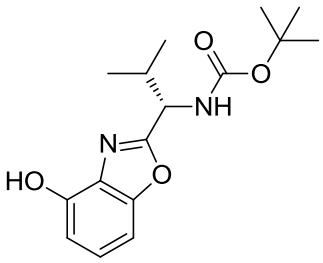
(*S*)-*tert*-Butyl (1-(4-hydroxy-1,3-benzoxazol-2-yl)-2-phenylethyl)carbamate (5.28)



5.28 was synthesised in an analogous method as **5.26**: To a solution of **5.22** (97 mg, 0.26 mmol) and triphenylphosphine (341 mg, 1.30 mmol) in tetrahydrofuran (4 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.260 ml, 1.30 mmol) dropwise. The mixture was stirred for 20 minutes at 0 °C and then allowed to warm to room temperature. Thin layer chromatography revealed the reaction to be complete after two hours. The solvent was removed under reduced pressure and product was purified twice using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:9 → 3:22→ 1:1 followed by silica gel eluting with ethyl acetate: dichloromethane 0:1 → 1:49→ 1:19→ 1:9), to yield a white solid (66 mg, 71%).

Mp 144–146 °C; $[\alpha]_D^{24}$ = –46.7 (*c* 0.107, $CHCl_3$); R_f = 0.47 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3348, 3144, 2981, 1688, 1616, 1525, 1451, 1251, 1165, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.32 (s, 9H, –C(C*H*$_3$)$_3$), 3.17–3.34 (m, 2H, –C*H*$_2$), 5.28–5.40 (m, 1H, –C*H*), 5.80 (d, *J* = 8.7 Hz, 1H, N*H*), 6.87 (d, *J* = 8.1 Hz, 1H, Ar–*H*), 6.97–7.08 (m, 3H, Ar–*H*), 7.13–7.24 (m, 4H, Ar–*H*), 8.85 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 28.4 (–C(*C*H$_3$)$_3$), 40.5 (–*C*H$_2$), 50.6 (–*C*H), 80.6 (–*C*(CH$_3$)$_3$), 102.6 (Ar–*C*), 111.3 (Ar–*C*), 126.3 (Ar–*C*), 127.1 (Ar–*C*), 128.6 (Ar–*C*), 129.0 (Ar–*C*), 129.4 (Ar–*C*), 135.8 (Ar–*C*), 148.2 (Ar–*C*), 151.8 (Ar–*C*), 155.5 (O–*C*=N), 164.7 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_4$: 355.1658; found: 355.1655.

(*S*)-*tert*-Butyl (1-(4-hydroxy-1,3-benzoxazol-2-yl)-2-methylpropyl)carbamate (5.29)

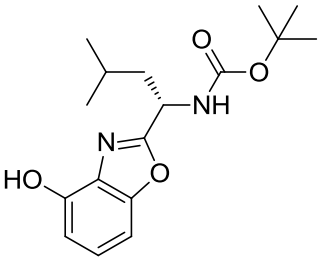


5.29 was synthesised in an analogous method as **5.26:** To a solution of **5.23** (77.5 mg, 0.240 mmol) and triphenylphosphine (312 mg, 1.19 mmol) in tetrahydrofuran (4 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.240 ml, 1.19 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. Thin layer chromatography revealed the reaction to be complete after two hours. The solvent was removed under reduced pressure and the product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:9), to yield a white solid (43 mg, 60%)

Mp 125–127 °C; $[\alpha]_D^{24}$ = –93.2 (*c* 0.118, $CHCl_3$); R_f = 0.34 (Ethyl acetate/hexane, 1:1); IR (ATR): 3279, 3139, 2973, 1698, 1613, 1505, 1368, 1245, 1160, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.92–1.01 (m, 6H, –CH(C*H*$_2$), 1.36 (s, 9H, –C(C*H*$_3$)$_3$), 2.17–2.34 (m,

1H, –C*H*$(CH_3)_2$), 4.92 (dd, *J* = 9.1, 6.4 Hz, 1H, –C*H*), 5.98 (d, *J* = 9.5 Hz, 1H, N*H*), 6.90 (d, *J* = 8.1 Hz, 1H, Ar–*H*), 6.98 (d, *J* = 8.0 Hz, 1H, Ar–*H*), 7.20 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 9.35 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 18.2 (–*C*H_3), 19.1 (–*C*H_3), 28.4 (–C(*C*$H_3)_3$), 33.2 (–*C*H$(CH_3)_2$), 54.9 (–*C*H), 80.3 (–*C*$(CH_3)_3$), 102.5 (Ar–*C*), 111.5 (Ar–*C*), 126.2 (Ar–*C*), 128.9 (Ar–*C*), 148.1 (Ar–*C*), 151.7 (Ar–*C*), 156.1 (O–*C*=N), 165.5 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{16}H_{23}N_2O_4$: 307.1658; found: 307.1666.

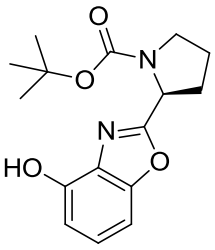
(S)-tert-Butyl (1-(4-hydroxy-1,3-benzoxazol-2-yl)-3-methylbutyl)carbamate (5.30)



5.30 was synthesised in an analogous method as **5.26:** To a solution of **5.24** (87 mg, 0.26 mmol) and triphenylphosphine (336 mg, 1.28 mmol) in tetrahydrofuran (4 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.250 ml, 1.28 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature. Due to problems with stirring more tetrahydrofuran (1 ml) was added to the thick yellow mixture. Thin layer chromatography revealed the reaction to be complete after three hours. The solvent was removed under reduced pressure and the product was purified using flash column chromatography (silica gel eluting with ethyl acetate: hexane 1:9), to yield a white solid (70 mg, 84%)

Mp 123–125 °C; $[\alpha]_D^{24}$ = –131.0 (*c* 0.526, $CHCl_3$); R_f = 0.36 (Ethyl acetate/hexane, 1:3); IR (ATR): 3363, 2968, 1683, 1623, 1534, 1459, 1189, 1133, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.96 (d, *J* = 6.2 Hz, 6H, –CH(C*H*$_3)_2$), 1.31 (s, 9H, –C(C*H*$_3)_3$), 1.62–181 (m, 3H, –C*H*$_2$ and –C*H*$(CH_3)_2$), 5.05–5.18 (m, 1H, –C*H*), 5.81 (d, *J* = 8.1 Hz, 1H, N*H*), 6.90 (d, *J* = 8.1 Hz, 1H, Ar–*H*), 7.02 (d, *J* = 8.1 Hz, 1H, Ar–*H*), 7.20 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 9.64 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 22.1 (–*C*H_3), 22.8 (–*C*H_3), 24.9 (–*C*H$(CH_3)_2$), 28.3 (–C(*C*$H_3)_3$), 43.8 (–*C*H_2), 48.0 (–*C*H), 80.2 (–*C*$(CH_3)_3$), 102.5 (Ar–*C*), 111.5 (Ar–*C*), 126.3 (Ar–*C*), 129.0 (Ar–*C*), 148.1 (Ar–*C*), 151.7 (Ar–*C*), 155.6 (O–*C*=N), 166.8 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{17}H_{25}N_2O_4$: 321.1814; found: 321.1819.

(S)-tert-Butyl 2-(4-hydroxy-1,3-benzoxazol-2-yl)pyrrolidine-1-carboxylate (5.31)

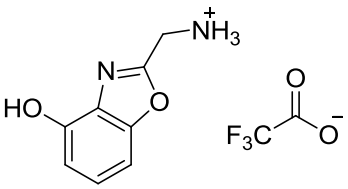


5.31 was synthesised in an analogous method as **5.26:** To a solution of **5.25** (154 mg, 0.480 mmol) and triphenylphosphine (150 mg, 0.570 mmol) in tetrahydrofuran (7.5 ml) at 0 °C was added di-isopropyl azodicarboxylate (0.11 ml, 0.57 mmol) dropwise. The mixture was stirred for 15 minutes at 0 °C and then allowed to warm to room temperature.

Thin layer chromatography revealed the reaction not complete after 25 hours and more triphenylphosphine (73 mg, 0.28 mmol) and di-isopropyl azodicarboxylate (0.060 ml, 0.28 mmol) were added to the mixture. 40 hours later the reaction was stopped. The solvent was removed under reduced pressure and the product was purified using flash column chromatography (silica gel eluting with ethyl acetate: heptane 1:7 → 3:17→ 7:33→ 1:4), to yield a white solid (93 mg, 64%).

Mp 158–160 °C; $[\alpha]_D^{24}$ = –120 (*c* 0.075, $CHCl_3$); R_f = 0.29 (Heptane/Ethyl acetate, 3:2); IR (ATR): 3362, 3148, 2976, 1696, 1613, 1450, 1388, 1249, 1189, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.16 and 1.37 (2xs, 9H, –C*H*$_3$), 1,87–2.49 (m, 4H, –C*H*$_2$), 3.43–3.77 (m, 2H, N–C*H*$_2$), 5.08–5.20 (m, 1H, N–C*H*), 6.82–6.93 (m, 1H, Ar–*H*), 7.04 (d, *J* = 8.1 Hz, 1H, Ar–*H*), 7.14–7.25 (m, 1H, Ar–*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 25 °C): δ = 24.2 (–*C*H$_2$), 28.3 (–C(*C*H$_3$)$_3$), 32.4 (–*C*H$_2$), 46.9 (N–*C*H$_2$), 55.3 (N–*C*H), 80.3 (–*C*(CH$_3$)$_3$), 102.3 (Ar–*C*), 111.3 (Ar–*C*), 126.2 (Ar–*C*), 129.0 (Ar–*C*), 148.5 (Ar–*C*), 151.7 (Ar–*C*), 154.0 (O–*C*=N), 166.7 (*C*=O); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}N_2O_4$: 305.1501; found: 305.1504.

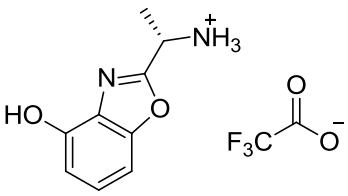
2-(Aminomethyl)-1,3-benzoxazol-4-ol trifluoroacetate (5.32)



Trifluoroacetic acid (0.13 ml, 1.8 mmol) was added to a solution of **5.26** (48 mg, 0.18 mmol) in dichloromethane (2 ml) at room temperature. After three hours more trifluoroacetic acid (0.13 ml, 1.8 mmol) was added to the solution and the reaction was followed to completion by thin layer chromatography (three hours) and the solvent removed under reduced pressure to leave a yellow oil. The oil was taken up in hexane (2 ml) and diethyl ether was added until a precipitate was formed. The off-white precipitate was collected and dried under high vacuum to yield **5.32** (40 mg, 80%).

Mp 153–156 °C (dec); R_f = 0.11 (methanol/dichloromethane, 1:19); IR (ATR): 3147, 1667, 1607, 1538, 1472, 1330, 1183, 1134, 1025 cm^{-1}; ^1H NMR (DMSO–D_6, 400 MHz, 25 °C): δ = 4.45 (s, 2H, –C*H*$_2$), 6.82 (d, *J* = 8.0 Hz, 1H, Ar–*H*), 7.15 (d, *J* = 8.1 Hz, 1H, Ar–*H*), 7.23 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 8.74 (br s, 3H, N*H*), 10.50 (br s, 1H, O*H*); ^{13}C NMR (DMSO–D_6, 100 MHz, 25 °C): δ = 36.0 (–*C*H$_2$), 101.4 (Ar–*C*), 110.5 (Ar–*C*), 126.4 (Ar–*C*), 128.8 (Ar–*C*), 149.7 (Ar–*C*), 152.1 (Ar–*C*), 158.0 (O–*C*=N); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_8H_8N_2O_2$: 165.0664; found: 165.0662.

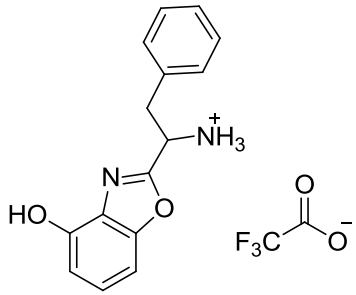
(*S*)-2-(1-Aminoethyl)-1,3-benzoxazol-4-ol trifluoroacetate (5.33)



Trifluoroacetic acid (0.340 ml, 4.62 mmol) was added to a solution of **5.27** (85.8 mg, 0.308 mmol) in dichloromethane (3.5 ml) at room temperature. The reaction was followed to completion by thin layer chromatography (four hours) and the solvent removed under reduced pressure to leave a colourless oil. The oil was taken up in hexane (3 ml) and diethyl ether was added until a precipitate was formed. The white precipitate was collected and dried under high vacuum to yield **5.33** (73 mg, 81%).

Mp 158–159 °C; $[\alpha]_D^{21}$ = –9.9 (*c* 0.101, MeOH); R_f = 0.17 (methanol/dichloromethane, 1:19); IR (ATR): 3371, 3206, 2931, 1671, 1622, 1461, 1184, 1134, 1045 cm^{-1}; ^{1}H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 1.65 (d, *J* = 6.9 Hz, 3H, –CH_3), 4.86 (q, *J* = 6.7 Hz, 1H, –C*H*), 6.83 (dd, *J* = 7.9, 0.9 Hz, 1H, Ar–*H*), 7.15 (dd, *J* = 8.2, 0.9 Hz, 1H, Ar–*H*), 7.24 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 8.85 (br s, 3H, N*H*), 10.55 (br s, 1H, O*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 17.1 (–*C*H_3), 44.2 (–*C*H), 101.4 (Ar–*C*), 110.5 (Ar–*C*), 126.5 (Ar–*C*), 128.8 (Ar–*C*), 149.8 (Ar–*C*), 152.1 (Ar–*C*), 158.2 ($J_{C\text{-}F}$ = 31.7 Hz, CF_3–*C*(O)), 161.0 (O–*C*=N); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_9H_{11}N_2O_2$: 179.0823; found: 179.0831.

(*Rac*)-2-(1-Amino-2-phenylethyl)-1,3-benzoxazol-4-ol trifluoroacetate (5.34)

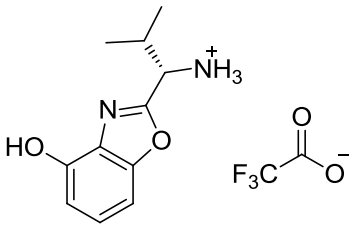


Trifluoroacetic acid (0.24 ml, 3.2 mmol) was added to a solution of **5.28** (79.2 mg, 0.213 mmol) in dichloromethane (2.2 ml) at 0 °C and warmed to room temperature. The reaction was followed to completion by thin layer chromatography (five hours) and the solvent removed under reduced pressure to leave a yellow oil. The oil was taken up in hexane (2 ml) and diethyl ether was added until a precipitate was formed. The white precipitate was collected and dried under high vacuum to yield **5.34** (68 mg, 86%).

Mp 174–177 °C (dec); R_f = 0.32 (methanol/dichloromethane, 1:19); IR (ATR): 3362, 2996, 2649, 1678, 1623, 1500, 1366, 1189, 1132, 1045 cm^{-1}; ^{1}H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 3.36 (m, 2H, –CH_2), 5.01 (dd, *J* = 8.1, 6.4 Hz, 1H, –C*H*), 6.80 (d, *J* = 7.6 Hz, 1H, Ar–*H*), 7.10 (d, *J* = 7.7 Hz, 1H, Ar–*H*), 7.13–7.32 (m, 6H, Ar–*H*), 8.91 (br s, 3H, N*H*), 10.52 (br s, 1H, O*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 37.6 (–*C*H_2), 49.5 (–*C*H), 101.5 (Ar–*C*), 110.5 (Ar–*C*), 117.3 ($J_{C\text{-}F}$ = 300.2 Hz, –*C*F_3), 126.7 (Ar–*C*), 127.3 (Ar–*C*), 128.7 (Ar–*C*), 128.8 (Ar–*C*), 129.3 (Ar–*C*), 134.6 (Ar–*C*), 149.8 (Ar–*C*), 151.9 (Ar–*C*), 158.0 ($J_{C\text{-}F}$ = 30.8

Hz, CF_3–*C*(O)), 159.6 (O–*C*=N); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}N_2O_2$: 255.1134; found: 255.1142.

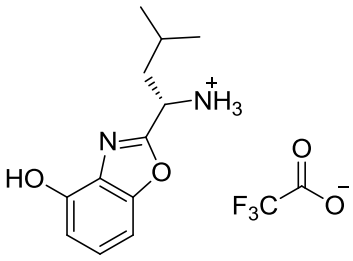
(*S*)-2-(1-Amino-2-methylpropyl)-1,3-benzoxazol-4-ol trifluoroacetate (5.35)



Trifluoroacetic acid (0.22 ml, 2.9 mmol) was added to a solution of **5.29** (73.2 mg, 0.216 mmol) in dichloromethane (2 ml) at 0 °C and warmed to room temperature. The reaction was followed to completion by thin layer chromatography (five hours) and the solvent removed under reduced pressure to leave a light yellow oil. The oil was taken up in hexane (2 ml) and diethyl ether was added until a precipitate was formed. The white precipitate was collected and dried under high vacuum to yield **5.35** (46 mg, 74%).

Mp 184–185 °C; $[\alpha]_D^{25}$ = –28.3 (*c* 0.106, MeOH); R_f = 0.27 (methanol/dichloromethane, 1:19); IR (ATR): 3364, 3059, 2992, 1678, 1623, 1501, 1187, 1133, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO–D_6, 400 MHz, 25 °C): δ = 0.67 (d, *J* = 6.8 Hz, 3H, –C*H*$_3$), 0.81 (d, *J* = 6.8 Hz, 3H, –C*H*$_3$), 2.11–2.23 (m, 1H, –C*H*$(CH_3)_2$), 4.10 (d, *J* = 6.0 Hz, 1H, –C*H*), 6.52 (d, *J* = 8.0 Hz, 1H, Ar–*H*), 6.68 (d, *J* = 8.0 Hz, 1H, Ar–*H*), 6.84 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 8.76 (br s, 3H, N*H* and O*H*); ^{13}C NMR ($CDCl_3$/DMSO–D_6, 100 MHz, 25 °C): δ = 17.2 (–*C*H_3), 18.2 (–*C*H_3), 30.5 (–*C*H$(CH_3)_2$), 53.9 (–*C*H), 101.0 (Ar–*C*), 110.2 (Ar–*C*), 115.6 ($J_{C\text{-}F}$ = 294.5 Hz, –*C*F_3), 125.7 (Ar–*C*), 128.4 (Ar–*C*), 149.2 (Ar–*C*), 151.7 (Ar–*C*), 158.9 (O–*C*=N), 160.0 ($J_{C\text{-}F}$ = 30.8 Hz, CF_3–*C*(O)); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{11}H_{15}N_2O_2$: 207.1134; found: 207.1141.

(*S*)-2-(1-Amino-3-methylbutyl)-1,3-benzoxazol-4-ol trifluoroacetate (5.36)

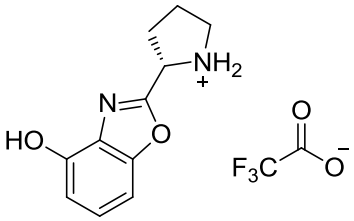


Trifluoroacetic acid (0.21 ml, 2.8 mmol) was added to a solution of **5.30** (59.3 mg, 0.185 mmol) in dichloromethane (2 ml) at room temperature. The reaction was followed to completion by thin layer chromatography (three hours) and the solvent removed under reduced pressure a colourless oil. The oil was taken up in hexane (2 ml) and diethyl ether was added until a precipitate was formed. The white precipitate was collected and dried under high vacuum to yield **5.36** (46 mg, 74%).

Mp 167–168 °C; $[\alpha]_D^{21}$ = –9.5 (*c* 0.105, MeOH); R_f = 0.27 (methanol/dichloromethane, 1:19); IR (ATR): 3363, 2968, 1683, 1623, 1502, 1189, 1133, 1046, 1046 cm^{-1}; ^{1}H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 0.89 (d, *J* = 6.6 Hz, 3H, –CH(C*H*$_3$)$_2$), 0.92 (d, *J* = 6.6 Hz, 3H, –

$CH(CH_3)_2$), 1.54–1.72 (m, 1H, –C*H*$(CH_3)_2$), 1.74–2.03 (m, 2H, –CH_2), 4.73 (dd, *J* = 8.0, 6.7 Hz, 1H, –C*H*), 6.83 (d, *J* = 8.0 Hz, 1H, Ar–*H*), 7.16 (d, *J* = 8.1 Hz, 1H, Ar–*H*), 7.24 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 8.84 (br s, 3H, N*H*), 10.58 (br s, 1H, O*H*); ^{13}C NMR (DMSO–D_6, 75.5 MHz, 25 °C): δ = 21.8 (–CH_3), 22.4 (–CH_3), 24.0 (–*C*H$(CH_3)_2$), 40.5 (–CH_2), 46.8 (–*C*H), 101.5 (Ar–*C*), 110.6 (Ar–*C*), 126.6 (Ar–*C*), 128.8 (Ar–*C*), 149.8 (Ar–*C*), 152.0 (Ar–*C*), 158.1 ($J_{C\text{-}F}$ = 31.1 Hz, CF_3–*C*(O)), 160.4 (O–*C*=N); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{12}H_{17}N_2O_2$: 221.129; found: 221.1306.

(*S*)-2-(Pyrrolidin-2-yl)-1,3-benzoxazol-4-ol trifluoroacetate (5.37)



Trifluoroacetic acid (0.20 ml, 2.6 mmol) was added to a solution of **5.31** (52.9 mg, 0.173 mmol) in dichloromethane (2 ml) at room temperature. The reaction was followed to completion by thin layer chromatography (five hours) and the solvent removed under reduced pressure to leave a yellow oil. The oil was taken up in hexane (2 ml) and diethyl ether was added until a precipitate was formed. The off-white precipitate was collected and dried under high vacuum to yield **5.37** (35 mg, 64%).

Mp 117–122°C; $[\alpha]_D^{29}$ = –12.9 (*c* 0.155, MeOH); R_f = 0.11 (methanol/dichloromethane, 1:19); IR (ATR): 3238, 3062, 1662, 1614, 1557, 1369, 1187, 1142, 1030, 999 cm^{-1}; ^{1}H NMR (DMSO–D_6, 300 MHz, 25 °C): δ = 1.99–2.16 (m, 2H, –CH_2), 2.29–2.49 (m, 2H, –CH_2), 3.31–3.43 (m, 2H, N–CH_2), 5.04 (t, *J* = 7.8 Hz, 1H, N–C*H*), 6.82 (dd, *J* = 8.0, 0.9 Hz, 1H, Ar–*H*), 7.17 (dd, *J* = 8.2, 0.9 Hz, 1H, Ar–*H*), 7.25 (t, *J* = 8.1 Hz, 1H, Ar–*H*), 9.45 (br s, 1H, –O*H*), 10.5 (br s, 2H, –N*H*); HRMS–ESI+: *m/z* $[M+H]^+$ calcd for $C_{11}H_{13}N_2O_2$: 205.0977; found: 205.0983.

General procedure for the antimicrobial testing

Clinical strains of *Escherichia coli* and *Staphylococcus aureus* were purchased from Pathcare. The Xenogen strains of *Pseudomonas aeruginosa (P. aeruginosa* X_{en5}*)* and *Staphylococcus aureus* (*S. aureus* X_{en31}) were purchased from Caliper Life Sciences.

E. coli and *P. aeruginosa* were grown in a Luria Broth under aeration and the *S. aureus* strains were grown in a brain-heart infusion broth, cultures were incubated for 24 hours at 37 °C (5 ml broth, cultures inoculated from glycerol stocks). Antimicrobial activity was determined using the ager well diffusion assay. Wells with a diameter of 7 mm were made in

Mueler Hinton agar, 100 µl culture was used to inoculate the agar and make spread plates of the respective cultures.

Approximately 20 µl of each compound was placed into each well; plates were inoculated at 37 °C for 24 hours, clear zones were indicative of antimicrobial activity.

Example of benzoxazole TFA salt ^{13}C NMR sprectra

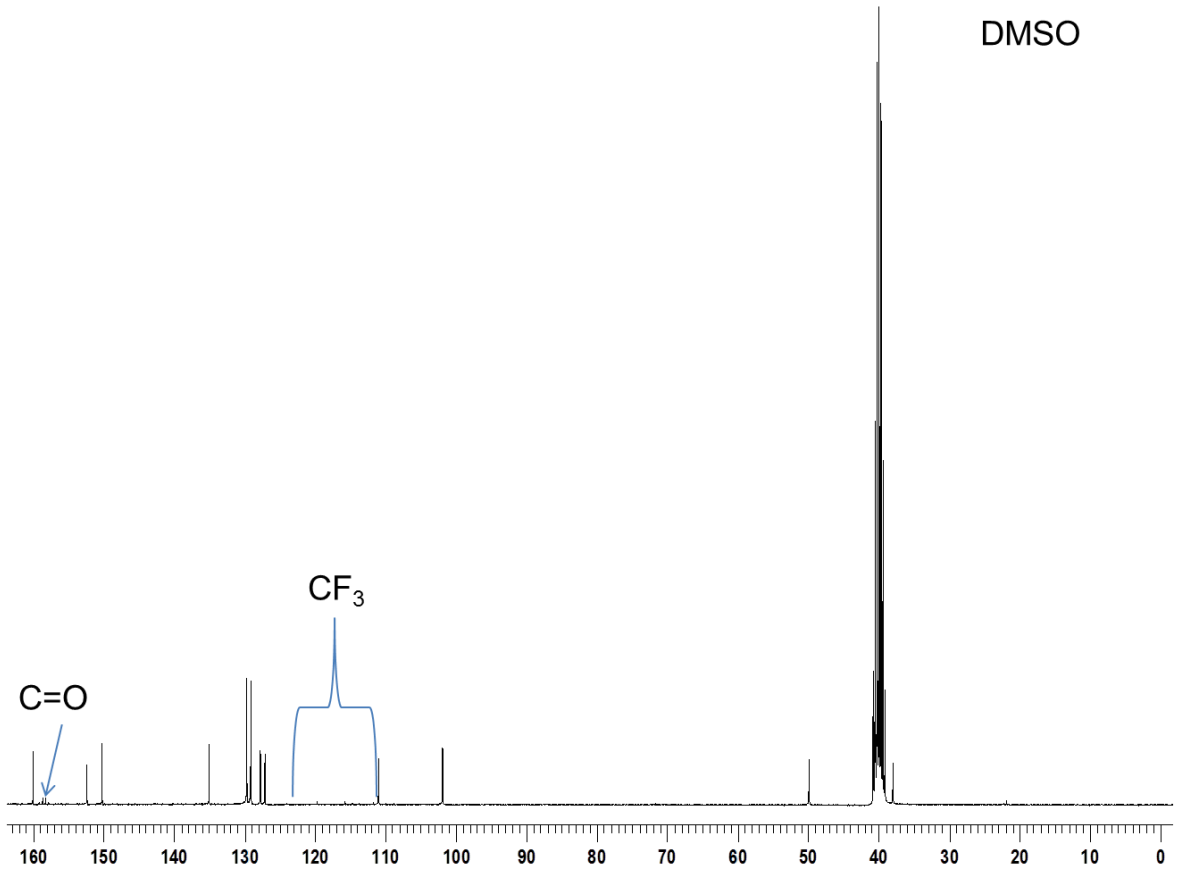


Figure 7.1 Example of a ^{13}C NMR spectrum of a benzoxazole TFA salt to show the relative position and amplitude of the TFA signals [*(Rac)*-2-(1-Amino-2-phenylethyl)-1,3-benzoxazol-4-ol trifluoroacetate (**5.34**) used as an example].

7.3 Crystal structures

A single crystal was covered in a small amount of paratone oil and mounted on a glass fibre. X-ray intensity data were collected at 100 K on a Bruker SMART APEX CCD with 1.75 kW graphite monochromated Mo radiation. The detector to crystal distance was 60 mm. Data were collected by omega scans. Data reduction and absorption corrections were carried out using the SAINT[19] and SADABS[20, 21] programmes, respectively. The structures were solved by direct methods or a combination of Patterson and partial structure expansion using SHELXS-97.[22] Non-hydrogen atoms were refined anisotropically by means of full-matrix least squares calculations on *F*2 using SHELXL-97 within the X-Seed[23] graphical user interface. Hydrogen atoms were placed on calculated positions.

2-Methyl-1,3-benzoxazol-4-ol (2.10)

Empirical formula	$C_8H_7NO_2$	
Formula weight	149.15	
Temperature (K)	173(2)	
Wavelength (Å)	0.71073	
Crystal system	triclinic	
Space group	*P*-1	
Unit cell dimensions (Å, °)	*a* = 5.348(4)	α = 92.721(9)
	b = 8.034(7)	β = 94.442(9)
	c = 17.564(14)	γ = 107.719(9)
Volume (Å)	714.6(10)	
Z	4	
Calculated density (g cm^{-3})	1.386	
Absorption coefficient (mm^{-1})	0.101	
F_{000}	312	
Crystal size (mm^3)	0.724 × 0.263 × 0.214	
θ range for data collection (°)	1.166 to 27.855	
Miller index ranges	$-6 \le h \le 7$, $-10 \le k \le 10$, $-21 \le l \le 22$	
Reflections collected	7471	
Independent reflections	3074 [R_{int} = 0.0210]	
Completeness to θ_{max} (%)	90.9	
Max. and min. transmission	0.7456 and 0.6704	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3074 / 0 / 210
Goodness-of-fit on F^2	1.069
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0366, $wR2$ = 0.0980
R indices (all data)	$R1$ = 0.0451, $wR2$ = 0.1039
Extinction coefficient	0.043(5)
Largest diff. peak and hole (e Å^{-3})	0.154 and -0.160

2-Benzyl-1,3-benzoxazol-4-ol (2.11)

Empirical formula	$C_{14}H_{11}NO_2$	
Formula weight	225.24	
Temperature (K)	100(2)	
Wavelength (Å)	0.71073	
Crystal system	triclinic	
Space group	*P*-1	
Unit cell dimensions (Å, °)	a = 5.4558(15)	α = 79.316(3)
	b = 9.827(3)	β = 85.884(3)
	c = 10.264(3)	γ = 78.111(3)
Volume (Å)	528.8(3)	
Z	2	
Calculated density (g cm^{-3})	1.414	
Absorption coefficient (mm^{-1})	0.095	
F_{000}	236	
Crystal size (mm^3)	0.271 × 0.254 × 0.121	
θ range for data collection (°)	2.020 to 28.276	
Miller index ranges	$-6 \le h \le 6$, $-12 \le k \le 13$, $-12 \le l \le 13$	
Reflections collected	6095	
Independent reflections	2370 [R_{int} = 0.0280]	
Completeness to θ_{max} (%)	90.4	
Max. and min. transmission	0.7456 and 0.6411	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2370 / 0 / 159	
Goodness-of-fit on F^2	1.044	
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0410, $wR2$ = 0.0940	
R indices (all data)	$R1$ = 0.0515, $wR2$ = 0.0999	
Extinction coefficient	0.025(5)	
Largest diff. peak and hole (e Å^{-3})	0.246 and -0.192	

Bis(2-Phenyl-1,3-benzoxazol-4-ol-κ^1*N*)dichloropalladium(II).CH_2Cl_2 (2.9a)

Empirical formula	$C_{27}H_{20}Cl_4N_2O_4Pd$	
Formula weight	684.65	
Temperature (K)	173(2)	
Wavelength (Å)	0.71073	
Crystal system	monoclinic	
Space group	*Pc*	
Unit cell dimensions (Å, °)	a = 11.7650(9)	α = 90
	b = 31.555(2)	β = 105.4450(10)
	c = 7.1302(5)	γ = 90
Volume (Å)	2551.4(3)	
Z	4	
Calculated density (g cm^{-3})	1.782	
Absorption coefficient (mm^{-1})	1.186	
F_{000}	1368	
Crystal size (mm^3)	0.250 × 0.250 × 0.030	
θ range for data collection (°)	1.291 to 28.683	
Miller index ranges	$-15 \le h \le 10$, $-34 \le k \le 42$, $-9 \le l \le 9$	
Reflections collected	16064	
Independent reflections	8824 [R_{int} = 0.0247]	
Completeness to θ_{max} (%)	92.4	
Max. and min. transmission	0.7457 and 0.6508	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8824 / 6 / 702	
Goodness-of-fit on F^2	1.021	
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0293, $wR2$ = 0.0643	
R indices (all data)	$R1$ = 0.0331, $wR2$ = 0.0663	
Extinction coefficient	.	
Largest diff. peak and hole (e Å^{-3})	0.584 and -0.628	
Absolute structure parameter	.44(3)	

Bis(2-Methyl-1,3-benzoxazol-4-ol-κ^1*N*)dichloropalladium(II).$2C_3H_7ON$ (2.10a)

Empirical formula	$C_{22}H_{28}Cl_2N_4O_6Pd$
Formula weight	621.78

Temperature (K)	173(2)	
Wavelength (Å)	0.71073	
Crystal system	triclinic	
Space group	*P*-1	
Unit cell dimensions (Å, °)	a = 6.4886(10)	α = 93.574(2)
	b = 9.4257(15)	β = 106.640(2)
	c = 10.7797(17)	γ = 94.730(2)
Volume (Å)	626.97(17)	
Z	1	
Calculated density (g cm^{-3})	1.647	
Absorption coefficient (mm^{-1})	0.998	
F_{000}	316	
Crystal size (mm^3)	0.250 × 0.250 × 0.040	
θ range for data collection (°)	1.980 to 28.725	
Miller index ranges	$-8 \leq h \leq 8$, $-12 \leq k \leq 12$, $-14 \leq l \leq 14$	
Reflections collected	7645	
Independent reflections	3006 [R_{int} = 0.0244]	
Completeness to θ_{max} (%)	92.5	
Max. and min. transmission	0.7458 and 0.6886	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3006 / 1 / 167	
Goodness-of-fit on F^2	1.072	
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0188, $wR2$ = 0.0479	
R indices (all data)	$R1$ = 0.0192, $wR2$ = 0.0481	
Extinction coefficient	.	
Largest diff. peak and hole (e Å^{-3})	0.468 and -0.698	

Bis(2-Phenyl-1,3-benzoxazol-4-ol-κ^1*N*)diacetatopalladium(II).3CH_2Cl_2 (2.9b)

Empirical formula	$C_{33}H_{30}Cl_6N_2O_8Pd$	
Formula weight	901.69	
Temperature (K)	173(2)	
Wavelength (Å)	0.71073	
Crystal system	monoclinic	
Space group	*C2/c*	
Unit cell dimensions (Å, °)	a = 14.2356(11)	α = 90
	b = 12.5410(10)	β = 102.5010(10)

	c = 20.3011(16)	γ = 90
Volume (Å)	3538.4(5)	
Z	4	
Calculated density (g cm^{-3})	1.693	
Absorption coefficient (mm^{-1})	1.032	
F_{000}	1816	
Crystal size (mm^3)	0.334 × 0.096 × 0.061	
θ range for data collection (°)	2.055 to 28.653	
Miller index ranges	$-18 \le h \le 18$, $-16 \le k \le 16$, $-26 \le l \le 26$	
Reflections collected	19584	
Independent reflections	4248 [R_{int} = 0.0277]	
Completeness to θ_{max} (%)	93.4	
Max. and min. transmission	0.9832 and 0.8687	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4248 / 0 / 261	
Goodness-of-fit on F^2	1.047	
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0233, *wR*2 = 0.0579	
R indices (all data)	*R*1 = 0.0270, *wR*2 = 0.0597	
Extinction coefficient	.	
Largest diff. peak and hole (e Å^{-3})	0.448 and -0.387	

Tetrakis(μ_2-2-Methyl-1,3-benzoxazol-4-olate)-dipalladium(II).$CH_3CN.4H_2O$ (2.10b)

Empirical formula	$C_{34}H_{35}N_5O_{12}Pd_2$	
Formula weight	918.47	
Temperature (K)	100(2)	
Wavelength (Å)	0.71073	
Crystal system	tetragonal	
Space group	*P4/ncc*	
Unit cell dimensions (Å, °)	*a* = 12.8613(12)	α = 90
	b = 12.8613(12)	β = 90
	c = 22.553(2)	γ = 90
Volume (Å)	3730.6(8)	
Z	4	
Calculated density (g cm^{-3})	1.635	
Absorption coefficient (mm^{-1})	1.032	
F_{000}	1848	

Crystal size (mm^3)	0.567 × 0.402 × 0.305
θ range for data collection (°)	1.806 to 28.850
Miller index ranges	$-16 \leq h \leq 17$, $-16 \leq k \leq 16$, $-30 \leq l \leq 30$
Reflections collected	41377
Independent reflections	2415 [R_{int} = 0.0214]
Completeness to θ_{max} (%)	98.1
Max. and min. transmission	1.0000 and 0.9234
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2415 / 2 / 134
Goodness-of-fit on F^2	1.036
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0193, *wR*2 = 0.0527
R indices (all data)	*R*1 = 0.0214, *wR*2 = 0.0541
Extinction coefficient	0.00032(6)
Largest diff. peak and hole (e $Å^{-3}$)	0.432 and -0.427

2-Methyl-1,3-benzoxazol-4-yl diphenylphosphinate (4.1)

Empirical formula	$C_{20}H_{16}NO_3P$	
Formula weight	349.31	
Temperature (K)	294(2)	
Wavelength (Å)	0.71073	
Crystal system	orthorhombic	
Space group	*Pbca*	
Unit cell dimensions (Å, °)	*a* = 9.4239(4)	α = 90.00
	b = 15.7574(6)	β = 90.00
	c = 23.5398(8)	γ = 90.00
Volume (Å)	3495.6(2)	
Z	8	
Calculated density (g cm^{-3})	1.327	
Absorption coefficient (mm^{-1})	0.176	
F_{000}	1456	
Crystal size (mm^3)	0.39 × 0.28 × 0.19	
θ range for data collection (°)	1.73 to 28.28	
Miller index ranges	$-9 \leq h \leq 12$, $-20 \leq k \leq 20$, $-31 \leq l \leq 27$	
Reflections collected	17408	
Independent reflections	4324 [R_{int} = 0.0477]	
Completeness to θ_{max} (%)	99.5	

Max. and min. transmission	0.9682 and 0.9341
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4324 / 0 / 229
Goodness-of-fit on F^2	1.009
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0466, $wR2$ = 0.0946
R indices (all data)	$R1$ = 0.1004, $wR2$ = 0.1173
Largest diff. peak and hole (e Å^{-3})	0.165 and -0.258

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